# THE American Journal OF Gastroenterology

VOL. 31, NO. 2 FEBRUARY, 1959

Panel Discussion on Diseases of the Esophagus

Duodenal Ulcer in Children

The Gastroenterological Aspects
of *Periarteritis Nodosa*

Ulcerative Colitis in a Southern General Hospital
and a Southern Industrial-Rural Area

***Twenty-fourth Annual Convention***
***Los Angeles, California***
***20, 21, 22, 23 September 1959***

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# THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

*The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada*

**contents:**

Editorial Board and General Information ..... 100
Panel Discussion on Diseases of the Esophagus
FRANZ J. INGLEFINGER, M.D., PHILIP KRAMER, M.D., LAMAR SOUTTER, M.D. and RICHARD SCHATZKI, M.D. 117
Duodenal Ulcer in Children.....JOSEPH SHAIKEN, M.D., F.A.C.G. 132
An Adjunct to Diagnosis of the Acute Perforation of the Upper Gastrointestinal Tract.....M. S. SAYDJARI, M.D., A. A. KANE, M.D., D.S., F.A.C.S., F.A.C.G., and S. MOLDIN, M.D. 141
The Use of Small Magnets to Locate the Tips of Tubes in the Gastrointestinal Tract Without Fluoroscopy.....SIDNEY FINK, M.D. and ROBERT VAUGHT 146
The Gastroenterological Aspects of *Periarteritis Nodosa*
EDWARD J. NIHGTINGALE, M.D., F.A.C.G., F.A.C.P. 152
Enzyme Activity in the Serum and Common Duct Bile of Dogs
HAROLD D. FRANKL, M.D. and JAMES H. MERRITT, B.S. 166
Clinical Evaluation of Paper Electrophoresis. VI. Normal Serum Lipid Partitions and Normal Serum Protein Fractions as a Function of Age and Sex.....A. ALLEN GOLDBLOOM, M.D., F.A.C.G., LINN J. BOYD, M.D., F.A.C.G. (Hon.), JOHN L. E. WOLFF, M.D. and SALVATORE BENTIVEGNA, M.D. 171
Ulcerative Colitis in a Southern General Hospital and a Southern Industrial-Rural Area.....JOHN M. MCMAHON, M.D., F.A.C.P., F.A.C.G. and BENJAMIN MORTON, M.D. 183
President's Message ..... 192
News Notes ..... 193
In Memoriam ..... 195
Abstracts for Gastroenterologists ..... 196

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## Index to Advertisers

Ames Co., Inc. 116
Ayerst Laboratories 210, 211
Desitin Chemical Co. 102
Eaton Laboratories 220
Geriatric Pharmaceutical Corp. 203
Lakeside Laboratories, Inc. 219
Lederle Laboratories 101, 206, 207
Mead Johnson 103
Merck Sharp & Dohme 114, 115, 204, 4th cover
Pfizer Laboratories 113
Purdue Frederick Co., The 215
Robins, A. H., Co., Inc. 212, 213
ROR Chemical Co. 195
Rorer, William H., Inc. 98
Searle, G. D., & Co. 97
Smith, Kline & French Laboratories 3rd cover
Squibb 104
Wallace Laboratories 208, 209, 214
Warner-Chilcott Laboratories 2nd cover
Winthrop Laboratories 217
Wyeth Laboratories 105, 106, 107, 108, 109, 110, 111, 112, 205, 218

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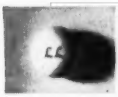
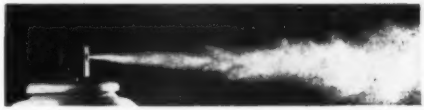
every  antibiotic

need  ...

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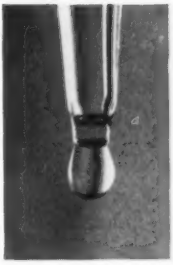
widely used  and

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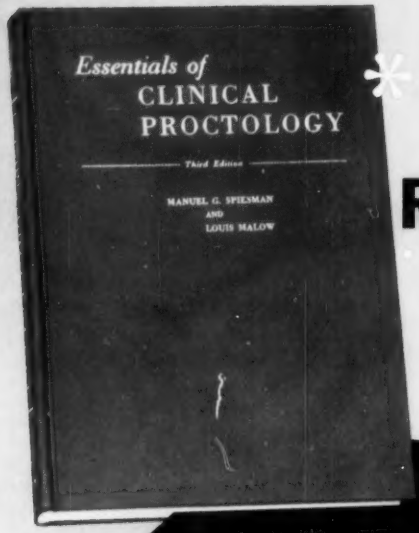


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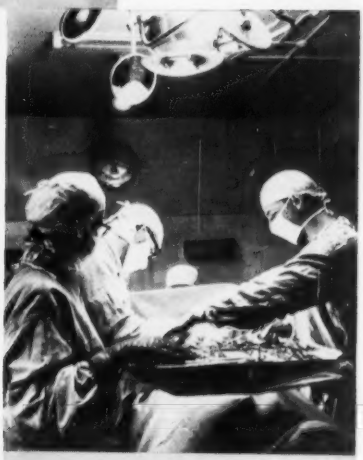

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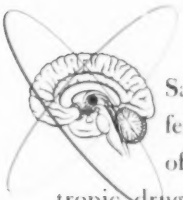

*new concept*

Satisfactory modification of the manifestations of abnormal brain activity is often achieved with individual psychotropic drugs acting on a single sector of the brain. In many patients, however, and despite high dosages, or change to another agent, response is only partial and is associated with lethargy and other more undesirable by-effects. Investigators have postulated that agents which will simultaneously alter the activity of more than one sector of the brain might produce a more satisfactory modification of undesirable emotional and behavioral patterns, thereby promoting a greatly improved total patient-response. To test this theory investigators recently have administered a low dosage of promazine, a phenothiazine, with a low dosage of meprobamate. The enhanced beneficial response elicited by this low-dosage dual attack is provided by PROZINE and warrants your consideration.

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# PROZINE*

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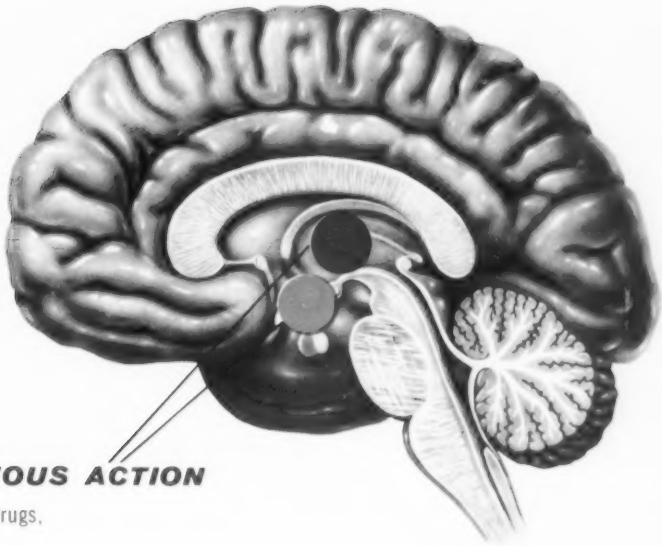

***SIMULTANEOUS ACTION***
of two psychotropic drugs,
affecting two areas
of the brain, produces
more ***SPECIFIC CONTROL***

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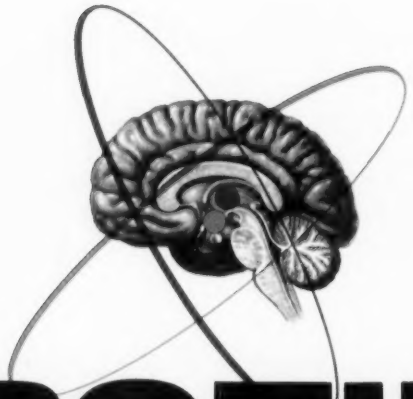

# PROZINE

## SPECIFIC CONTROL THROUGH DUAL ACTION

The physician will see many applications for PROZINE in his day to day practice, particularly in overly apprehensive medical patients (including surgical and obstetrical cases) and in the management of emotional problems of children, adolescents and the aged; also in emotionally disturbed patients who receive little or no relief from analgesics, barbiturates, anticholinergics, antihypertensives, hormones (estrogens and corticoids). The dosages of these drugs may be dramatically reduced.

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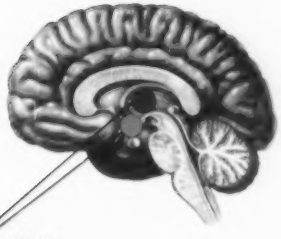

***SIMULTANEOUS ACTION***
of two psychotropic drugs,
affecting two areas
of the brain, produces
more ***SPECIFIC CONTROL***

*with minimal side-effects*

**IN 972 PATIENTS ON PROZINE—**
patients with emotional disturbances, or with organic diseases and emotional disturbances, or with psychotic illnesses
**INCIDENCE OF SIDE-EFFECTS WAS 3.7%**

# PROZINE

# PROOF OF CLINICAL EFFECTIVENESS—RES

| PRIMARY EMOTIONAL DISTURBANCE | | | | | | | | | | | ORGANIC DISEASE WITH EMOT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Capsules per Day | | Duration of Treatment | | | Result | | | SIDE EFFECT | | | Capsules per Day | | D T |
| | No. | 1-3 | 4-6 | Days 1-7 | Wks. 1-4 | Mos. 1-6 | IMPROVED | SAME | WORSE | | | No. | 1-3 | 4-6 | Days 1-7 |
| **Anxiety Neurosis** with Nausea, Vomiting, Fear, Tremor, Palpitations | 74 | 37 | 37 | 15 | 53 | 6 | 62 | 12 | — | 7 | **Gastrointestinal** Peptic Ulcer Colitis Steatorrhea | 48 | 26 | 22 | 5 |
| **Anxiety Reaction** with Headache or Migraine | 20 | 10 | 10 | 3 | 15 | 2 | 16 | 4 | — | 1 | **Cardiovascular** Hypertension Angina Pectoris | 33 | 9 | 24 | 3 |
| **Anxiety Reaction** causing Insomnia | 24 | 16 | 8 | 2 | 20 | 2 | 20 | 3 | 1 | 2 | **Dermatological** Neurodermatitis Eczema Pruritus | 34 | 2 | 32 | 3 |
| **Apprehension and Tension** | 14 | 2 | 12 | 1 | 9 | 4 | 12 | 2 | — | — | **Musculoskeletal** Rheumatoid Arthritis Osteoarthritis Traumatic Arthritis Myositis | 32 | 10 | 22 | 3 |
| **Depression** with Anxiety | 30 | 15 | 15 | 4 | 18 | 8 | 21 | 9 | — | — | **Endocrine** Hyperthyroidism Hypothyroidism Diabetes Mellitus | 11 | 5 | 6 | 1 |
| **Psychoneurosis** | 32 | 7 | 25 | 9 | 18 | 5 | 25 | 6 | 1 | 4 | **Menopausal Syndrome** | 28 | 10 | 18 | 2 |
| **Pregnancy** Nausea and Vomiting | 53 | 51 | 2 | 3 | 50 | — | 45 | 7 | 1 | — | **Allergic** Hay Fever Asthma | 15 | 12 | 3 | 9 |
| **Preoperative Medication** | 7 | 7 | — | 7 | — | — | 7 | — | — | — | **Carcinoma** | 6 | 1 | 5 | 1 |
| **Alcoholism** | 66 | 7 | 59 | 14 | 41 | 11 | 56 | 8 | 2 | — | **Chronic Brain Syndrome** | 19 | 15 | 4 | — |
| **Claustrophobia** | 3 | 1 | 2 | 1 | 2 | — | 3 | — | — | — | **Mentally Retarded** (Disturbed) | 96 | 54 | 42 | — |
| **Hypochondriasis** | 1 | 1 | — | 1 | — | — | — | 1 | — | — | **Impotency** | 1 | 1 | — | 1 |
| **Juvenile Delinquency** | 98 | 48 | 50 | — | — | 98 | 82 | 16 | — | — | | | | | |
| Total | 422 | | | | | | | | | 14 | | 323 | | | |

# RESPONSE IN 972 PATIENTS† ON PROZINE

| EMOTIONAL DISTURBANCE | | | | | | | PSYCHOTIC ILLNESS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Duration of Treatment | | | Result | | | SIDE EFFECT | | | Capsules per Day | | | Duration of Treatment | | | Symptomatic Response | | | SIDE EFFECT |
| Days 1-7 | Wks. 1-4 | Mos. 1-6 | IMPROVED | SAME | WORSE | | | No. | 1-3 | 4-6 | 7-10 | Wks. 0-4 | Months 1-3 | 3-6 | IMPROVED | SAME | WORSE | |
| 5 | 24 | 19 | 41 | 7 | – | 1 | Postpartum Psychosis | 2 | 1 | – | 1 | 1 | 1 | – | 1 | 1 | – | – |
| 3 | 19 | 11 | 28 | 4 | 1 | 2 | Behavioral Problem (Psychotic) | 5 | 3 | 2 | – | 3 | 2 | – | 4 | 1 | – | – |
| 3 | 27 | 4 | 21 | 9 | 4 | 6 | Manic Depression | 20 | 13 | 3 | 4 | 13 | 7 | – | 13 | 7 | – | – |
| 3 | 13 | 16 | 27 | 4 | 1 | – | Schizophrenia<br>Chronic Undifferentiated<br>Hebephrenic<br>Paranoid<br>Catatonic<br>Mixed | 175 | 79 | 56 | 40 | 31 | 138 | 6 | 108 | 63 | 4 | 8 |
| 1 | 6 | 4 | 10 | 1 | – | – | Involutional Psychosis | 9 | 3 | 5 | 1 | 4 | 1 | 4 | 7 | 2 | – | – |
| 2 | 8 | 18 | 27 | 1 | – | – | Phobic Reaction | 6 | 2 | 4 | – | 5 | 1 | – | 3 | 3 | – | – |
| 9 | 4 | 2 | 7 | 6 | 2 | 2 | Undifferentiated Psychosis | 4 | 2 | 2 | – | 1 | 3 | – | 1 | 3 | – | 1 |
| 1 | 2 | 3 | 5 | 1 | – | 1 | Obsessive Compulsive | 2 | – | 2 | – | 2 | – | – | 1 | 1 | – | – |
| – | 9 | 10 | 14 | 5 | – | – | Senile Psychosis | 4 | 4 | – | – | 3 | 1 | – | 4 | – | – | – |
| – | – | 96 | 84 | 11 | 1 | 1 | | | | | | | | | | | | |
| 1 | – | – | – | 1 | – | – | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | 13 | | 227 | | | | | | | | | | 9 |

# PROOF OF MINIMAL SIDE-EFFECTS—

# ONLY 3.7% IN 972 PATIENTS† ON PROZINE

| | Anxiety Neurosis | Anxiety Reaction with Headache | Anxiety Reaction with Insomnia | Psycho-neurosis | Gastro-intestinal Disorders | Cardio-vascular Disease | Dermato-logical Disorders | Allergic Conditions | Carcinoma | Mentally Retarded | Schizo-phrenia | Undiffer-entiated Psychosis | Total Each Group |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fatigue Lethargy | 5 | | 1 | 1 | | | 1 | | 1 | | | | 9 |
| Confusion Euphoria | | | | | | | 2 | | | | | | 2 |
| Vertigo | | | | | 1 | | | | | | | | 1 |
| Epigastric Distention | 1 | 1 | | 2 | | | 1 | | | | | 1 | 6 |
| Burning in Throat | | | | | | | 1 | 1 | | | | | 2 |
| Nausea Vomiting | | | 1 | | | | | | | | 2 | | 3 |
| Rash | | | | | | | 1 | | | 1 | 4 | | 6 |
| Flare-up Eczema | | | | | | | | 1 | | | | | 1 |
| Dryness of Mouth | 1 | | | | | 2 | | | | | | | 3 |
| Mild Hypotension | | | | | | | | | | | 2 | | 2 |
| Panic Reaction | | | | 1 | | | | | | | | | 1 |
| | | | | | | | | | | | | Total | 36 |

The occurrence of slight drowsiness in the first 48 hours of treatment indicates the dose prescribed is in excess of the patient's requirements and is not regarded as a side-effect of Prozine.

Incidence of Side-Effects **3.7%**

†Data from 972 case reports on file at Wyeth Laboratories

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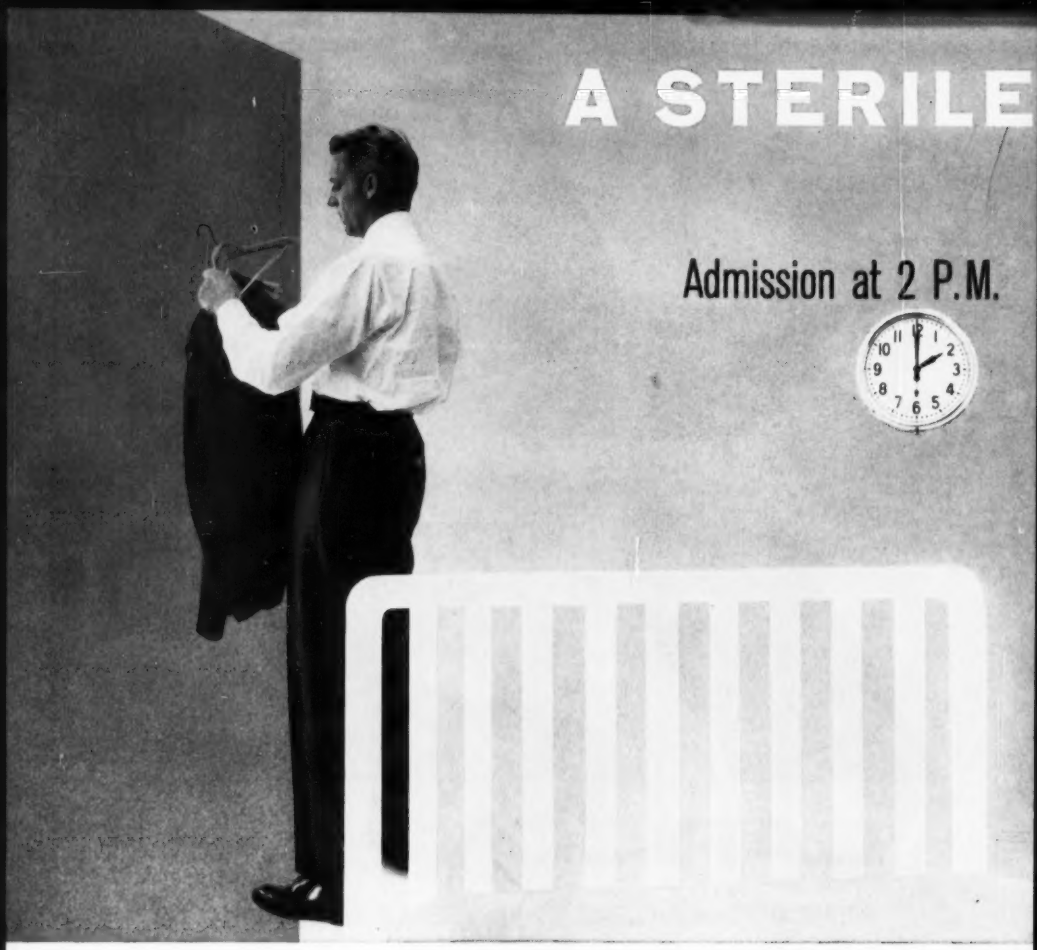


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1. Poth, E. J.: Intestinal Antisepsis in Surgery, J.A.M.A. 153:1516, Dec. 26, 1953.

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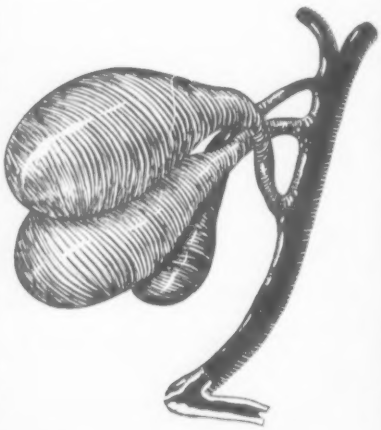
*Source:* Skilboe, B.: Am. J. Clin. Path. *30*:252, 1958.



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(1) Beckman, H.: Drugs: Their Nature, Action and Use, Philadelphia, W. B. Saunders Company, 1958, p. 425.
(2) Biliary Tract Diseases, M. Times *85*:1081, 1957.

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# PANEL DISCUSSION ON DISEASES OF THE ESOPHAGUS*

FRANZ J. INGELFINGER, M.D., *Moderator*†
PHILIP KRAMER, M.D.‡
LAMAR SOUTTER, M.D.¶
and
RICHARD SCHATZKI, M.D.§
Boston, Mass.

*Dr. Franz J. Ingelfinger:*—We will attempt to make this an informal panel, with questions and answers. It is unrehearsed. I am going to ask some questions to which there are really no final answers, but since this is an audience composed of sophisticated gastroenterologists, we do not have to emphasize some of the more obvious aspects of our subject.

First I should like to introduce the gentleman on my right. We now look the same as viewed from above; nevertheless, he was my teacher at one time, Dr. Richard Schatzki, and I am still a little bit afraid of him. I am not afraid of the other two gentlemen, Dr. Lamar Soutter, on my immediate left, and Dr. Philip Kramer, because they are long-time friends and associates of mine. I will not give their titles. They are known to you, and the titles are in the program anyway.

Dr. Schatzki, you, as a radiologist, must depend on anatomy, and I will start by asking you a simple anatomical question, namely: where does the esophagus end and the stomach begin?

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*Dr. Richard Schatzki:*—That is a very simple question? Of course, some of you will know that is about the most tricky question one could possibly be asked, because volumes have been written about it and people have been fighting for the last hundred years about that.

There are various differential points which have been used and which may be used for answering this question. One answer is that it is the point where the gastric and esophageal mucosae meet. That sounds very obvious. Another point is where the muscularis of the esophagus changes into the muscularis of the stomach. Another point of differentiation is where the peritoneum starts, and, finally, and I think probably the simplest, easiest and most reliable in many respects, is where the cylinder changes into a bag; and that just about covers it, Dr. Ingelfinger.

*Dr. Ingelfinger:*—Which definition do you like best?

*Dr. Schatzki:*—The last one, for all practical purposes.

*Dr. Ingelfinger:*—How about you, Dr. Soutter? Do you have any strong feelings as to how to define the end of the esophagus and the beginning of the stomach?

*Dr. Lamar Soutter:*—I do not have any strong feelings except that from the surgical viewpoint one thing might be mentioned: the longitudinal muscle fibers of the esophagus extend down on the lesser curvature of the stomach for a short distance, and that is the point at which the stomach wall is weakest. Consequently, if the stomach ever gets distended with oxygen or air, as I have seen happen twice accidentally, that is where it will rupture.

*Dr. Philip Kramer:*—I agree with Dr. Schatzki but would like to add one more criterion. On manometric studies one finds a zone of high pressure in the lower 2-4 cm. of the esophagus. The pressure obtained exceeds that found in the esophagus proper above and the stomach distally. I think that the esophagogastric junction is at that point where the high pressure zone ends.

*Dr. Schatzki:*—May I add one thing?

*Dr. Ingelfinger:*—Disagree, of course, if you want to.

*Dr. Schatzki:*—I disagree with the question. I say the question is one which leads to hours of discussion and fight, but not to a solution because as far as the gastroesophagic junction is concerned, it is wherever those discussing it agree upon. So far as I can see, the important thing is that those making the discussion agree on what they want to call the esophagus and what they want to call the stomach.

*Dr. Ingelfinger:*—Well, we have agreed fairly well that the junction is where the cylinder of the esophagus widens into the sac of the stomach. As Dr. Schatzki

has pointed out, there are statements in the literature, and some of them most vehement, that the esophagus and stomach meet at their mucosal junction, and that anything lined with gastric mucosa is necessarily stomach, and anything lined with esophageal mucosa, esophagus. This definition, however, puts one into a pretty difficult position. The mucosal junction may be of importance, to be sure, for evaluating esophagitis and the kind of secretions that the mucosa produces, but if we go into comparative anatomy, we see that in some animals, such as the horse, esophageal mucosa extends quite far down into what is essentially a big monolocular stomach. Does this mean that the horse's stomach is really esophagus?

Now, Dr. Kramer, I am going to ask you about the high pressure zone which you previously mentioned as situated in the distal esophagus. What is the function of this zone, and do you think there are sphincters at either the upper or lower end of the esophagus? I also wasn't quite sure where you meant this high pressure zone was in relation to the gastroesophageal junction.

*Dr. Kramer:*—At the upper end, opposite the sixth cervical vertebra posteriorly and the cricoid anteriorly there is a circular muscular structure called the cricopharyngeus. It is formed by the lower fibers of the inferior constrictor muscle. I believe this is the upper esophageal sphincter.

In the lower 2-4 cm. of the esophagus there exists the high pressure zone mentioned previously. The motor function of this zone differs from the esophagus proximally and the stomach distally. It can contract and relax reflexly. Radiographically it appears contracted initially on a barium swallow. It is my belief that this is an intrinsic sphincter, i.e., the lower esophageal sphincter. It is probably one of the three mechanisms by which gastroesophageal reflux is prevented.

*Dr. Ingelfinger:*—Dr. Soutter, do you see any evidence of this sphincter when you use an esophagoscope?

*Dr. Soutter:*—No.

*Dr. Ingelfinger:*—Why not?

*Dr. Soutter:*—In inserting the esophagoscope into the cricopharyngeus, the resistance of this muscle may, it is true, be felt. Sometimes it will not open up, and you first have to pass a small bougie through and follow it down with the esophagoscope to avoid undue trauma. The people I examine are nearly always under some form of narcosis, usually a barbiturate and some morphine, and this will cause relaxation.

*Dr. Ingelfinger:*—Didn't Chevalier Jackson call the cricopharyngeus the "gate of tears" of the inexperienced gastroscopist?

*Dr. Soutter:*—He was quite right.

*Dr. Ingelfinger:*—Do you ever face the same problem in passing the lower sphincter of the esophagus?

*Dr. Soutter:*—The problem there is more one of esophageal angulation and trying to pass the esophagoscope around curves when they occur, and that requires, I think, a great deal of judgment. As I watch young residents and try to teach them how to do esophagoscopy, I teach them to try to keep the patient's head in line with the esophagus, so that they are not bearing forcibly with the stiff-ended esophagoscope. In older people, with rigid spine and neck, you may have to terminate esophagoscopy at about the level of the stomach because you are unable to get around the angles. The presence of the muscle obstructing passage of the gastroesophageal junction, however, does not seem obvious.

*Dr. Ingelfinger:*—Unlike many of you in this audience, I am not allowed to pass an esophagoscope, at least at our hospital. We medical men have to let the thoracic surgeon do that. I say this without rancor because I am delighted to have Dr. Soutter's assistance and association in this work, but my impressions are gained therefore from what I sometimes see over a big shoulder.

Dr. Soutter, don't you sometimes see, as you approach the lower part of the esophagus and advance the scope cautiously, a rosette with a puckering, as if there were a closure in that area?

*Dr. Soutter:*—It is fairly rare in my experience. I must admit a lot of the older people I esophagoscope are under general anesthesia. Possibly the muscle relaxation, from whatever the anesthetist gives them, may prevent the rosette from appearing.

I don't believe in gastroenterologists performing esophagoscopy. I don't think you are too old to learn, but we wouldn't encourage you.

*Dr. Ingelfinger:*—Dr. Schatzki, what do you feel, from the radiologist's standpoint? Do you think it is a lot of folderol, or is there really something you can see that suggests an intrinsic lower esophageal sphincter? Some of you may have read the article by Nauta of Holland, wherein he reports putting metal markers in dogs on the diaphragmatic hiatus, on the mucosa of the esophagus, and on the serosa of this organ. Then, after watching the metal markers move as the dog swallowed, and taking moving pictures of the fluoroscopic image, he came to the conclusion that there was no really different mechanism at the lower end of the esophagus. Do you think that is true? I realize this is a very controversial issue. I want your own opinion.

*Dr. Schatzki:*—I have been for many years convinced that there is an internal sphincter mechanism in the lower end of the esophagus. Probably the easiest thing here is to show a slide. Normally you cannot see evidence of a sphincter during x-ray examination because normally it lies within the hiatus. But, if the stomch extends above the hiatus and is filled, one sees very frequently

something similar to what you see here, namely a constricting mechanism about half a centimeter to a centimeter in length. I have the impression it is very weak and, physiologically, a very insufficient type of constrictor, but it seems to me very definitely there.

*Dr. Ingelfinger:*—In a situation like that, and the patient examined when lying down, when the pouch above the diaphragm fills, do you find evidence that this zone can prevent reflux from the pouch into the esophagus above, or does the constriction come and go?

*Dr. Schatzki:*—It is a little difficult to answer that question. My impression is that it very rarely prevents reflux.

*Dr. Ingelfinger:*—Under these conditions of diaphragmatic hernia, then, you would not ascribe much efficiency to the sphincter in preventing reflux?

*Dr. Schatzki:*—With a little grain of salt, I think it does to a certain degree have an influence in preventing reflux. Under normal conditions, however, it is a little difficult for me to assume that it is the only mechanism preventing gastroesophageal reflux.

*Dr. Ingelfinger:*—Let's finish up the physiologic issues by considering the various mechanisms believed to prevent reflux. There is first the sphincter; second, the flap valve formed, it is stated, by the junction of the medial wall of the stomach and the lateral wall of the esophagus, meeting in a "V" and flapping over and closing the esophageal orifice in a passive way; third, there are the mucosal folds puckered up into a rosette; and fourth there is the diaphragm.

Dr. Kramer, do you think these are all equally active, or do you have any strong feeling that one is more important than the other?

*Dr. Kramer:*—The main feeling I have is that the diapragm has very little to do with it.

*Dr. Schatzki:*—Why?

*Dr. Kramer:*—The gastroesophageal junction has been transplaced above the diaphragm and still the sphincter mechanism holds. This has been proved in experimental animals, i.e. dogs.

*Dr. Schatzki:*—As well as if the sphincter is placed below the diaphragm?

*Dr. Kramer:*—Yes.

*Dr. Ingelfinger:*—Do you have any statement you want to make on this, Dr. Soutter?

*Dr. Soutter:*—From my experience of replacing the esophagus where it belongs, in repairing hiatus hernia, I have a feeling that resistance to reflux is better when the gastroesophageal junction is below the diaphragm, and when we close the hiatus fairly tightly. In surgery, we are doing something that

changes the nature of the diaphragm as it pulls upon the esophagus, although we are not restoring anatomical relationships to normal, i.e. before the development of the hiatus hernia. Nevertheless, it seems to me that resistance to reflux is better when normal relationships are restored, and the only thing that explains this improvement would appear to be the effect of the diaphragm on the esophagus.

*Dr. Schatzki:*—That the diaphragm has some influence in the prevention of reflux has been shown experimentally in dogs. Cutting of the crus of the diaphragm without touching the esophagus produced reflux esophagitis.

*Dr. Kramer:*—My impression is that the crus has an important function in that it angulates the esophagus during inspiration. I don't think it functions otherwise in preventing reflux from the stomach.

*Dr. Ingelfinger:*—If I may take the liberty of speaking on this a little bit, I should like to say that from the same clinic, the Mayo Clinic, within the course of less than two years two articles have appeared, the first of which was in the category Dr. Schatzki mentioned. In dogs, the authors cut the crus, or moved the junctional zone above the diaphragm, and concluded that reflux was so potentiated, particularly as evidenced by increased signs of esophagitis. Parenthetically, I think it is important to realize how reflux is measured in some of these studies.

On the basis of this paper, Dr. Johnstone of England said that the diaphragm had now been proved to play *the* role in preventing reflux and that there was no need for intraluminal manometry or other studies.

The second paper, referred to by Dr. Kramer, reported exactly opposite findings in dogs also exposed to various manipulations in the hiatal area. So take your choice: you can cite those dog experiments that support your view.

Agreement does not even exist as to whether or not the diaphragmatic hiatus contracts on inspiration. Dr. Schatzki, you once mentioned that if you put a finger up into the hiatus of a patient being operated upon, you could feel your finger being squeezed as the patient breathed in. In a recent review of the literature, I came across some interesting data on this point, namely, eleven reports of what happens when one puts a finger, or a balloon, in the hiatus of anesthetized human beings or animals via a gastrostomy, and feels what happens as the diaphragm descends on inspiration. Five said it pinched, and six said it didn't. Take your choice.

I now predict Dr. Schatzki will show us a picture of the esophagus in a patient who is inspiring forcefully.

*Dr. Schatzki:*—Yes, I think that anyone who is doing fluoroscopy and noting what happens cannot deny that on inspiration the esophageal lumen within the hiatus is smaller than on expiration. Of course, one may ask: Is the respiratory

narrowing of the esophagus directly caused by the action of the diaphragm, or indirectly by stimulation of a localized sphincteric mechanism in the lower esophagus? If it were due to stimulation of such an intrinsic sphincteric mechanism, no inspiratory narrowing of the gastrointestinal tube should occur at the hiatus in hiatus hernia where the lower end of the esophagus no longer lies in the hiatus. The same squeezing mechanism of the diaphragm can, however, be observed during inspiration, this time on the stomach rather than on the esophagus.

*Dr. Ingelfinger:*—One more explanation is given for the apparent arrest of esophageal transport on deep inspiration. When you breathe in, as the patient did in the slide shown, you also decrease intrathoracic pressure and increase intraabdominal pressure. It has been argued that the barium swallow appears to be stopped just above the diaphragm only because you produce such a high gastroesophageal pressure gradient that the material in the esophagus cannot be pushed into the stomach.

I think we may conclude that the medical profession does not really know the mechanisms that prevent reflux. The diaphragm, directly or indirectly, must play some role, if for no other reason than that repair of hernias tends to lessen reflux.

Let's go on to some clinical categories. Dr. Kramer, what do you consider the chief symptoms of esophageal disease? Tell us what you think about dysphagia, pain and heartburn.

*Dr. Kramer:*—The most important symptom is dysphagia, and that means an actual impediment to the passage of food. The passage of food is delayed somewhere in the esophagus, and the patient has a sensation as if it is sticking there. This does not necessarily mean that it is painful. Definite dysphagia should be very thoroughly investigated and not dismissed.

People frequently say they have "a lump" in their throat, especially when in the state of nervous indecision, or the state of emotional upset. When they swallow, they have no impediment or alteration in the passage of food, and therefore do not have any trouble swallowing. It is just a sensation, "a lump in the throat".

Heartburn is also a very important symptom. To me heartburn means reflux, i.e., acid reflux into the esophagus from the stomach. I do not know the exact pathophysiology. Some investigators say it is due to spasm; others say it is due to irritation. It has been said that a patient with achlorhydria may have heartburn. I wonder how thoroughly these patients have been investigated.

Another symptom is pain, and usually the pain is substernal and coincides with the site of the lesion. It may not, however, necessarily be so, because sometimes a lesion low down in the esophagus may give a sensation of pain high up in the throat or even in the ear, and sometimes a lesion high up in the esophagus

may give discomfort or pain low down. This pain is usually associated with swallowing.

So far as belching is concerned, I think this is a nonspecific symptom. Practically every functional gastroenterological patient has belching.

*Dr. Ingelfinger:*—Do you think it is fair to say that dysphagia is fairly specific for esophageal disease?

*Dr. Kramer:*—Yes.

*Dr. Ingelfinger:*—Do you think dysphagia is caused by heart disease?

*Dr. Kramer:*—There are vascular lesions which cause compression of the esophagus, e.g., *dysphagia lusoria* due to an arterial anomaly. Rheumatic heart disease associated with mitral stenosis and a large left auricle may also compress the esophagus.

*Dr Ingelfinger:*—How about an aneurysm of the aorta?

*Dr. Kramer:*—Aneurysm may cause dysphagia.

*Dr. Ingelfinger:*—I think you have done considerable work in investigating pain in the lower thorax by balloon distention. We are all faced with the problem of interpreting pain in the lower thorax and in deciding whether it is caused by heart disease, esophageal disorder, diaphragmatic hernia, or possibly gallbladder trouble; and it has been suggested that a balloon be put into the esophagus or hernia to distend the organ. If pain so produced is similar to the spontaneous pain of the patient, it is presumed to be of esophageal or hernial origin. If it is different, it is concluded that the spontaneous pain arises in the heart or elsewhere.

Is that a very good test?

*Dr. Kramer:*—In my opinion it is not very good. We studied 19 patients with angina pectoris, all with positive electrocardiographic abnormalities, and we discovered in distending the lower esophagus in these 19 patients, 7 of the 19 could not distinguish between their anginal pain and the pain produced by esophageal distention. At the same time the esophagus was being distended, we took electrocardiograms, which, since they showed no acute changes—indicated that the patients were not having anginal pain because of psychic or emotional distress.

On the other hand, we examined 10 patients with definite esophageal disease and distended the esophagus with a balloon. In 4 of the 10, the pain so produced was entirely different from their spontaneous pain. Balloon distention of the esophagus was thus of not much value in determining the origin of lower substernal pain.

*Dr. Ingelfinger:*—In these patients, the esophagus was distended in the general area of the esophageal disease?

*Dr. Kramer:*—Yes.

*Dr. Ingelfinger:*—Do you have comments, Dr. Schatzki, on dysphagia, or any of the symptoms we have been discussing?

*Dr. Schatzki:*—One thing Dr. Kramer brought out was the definition. He spoke of the fact that someone has dysphagia when he can't get the food down. Pain may or may not be present with dysphagia.

*Dr. Ingelfinger:*—On the basis of history alone, Dr. Kramer, how often do you think you can make a correct diagnosis of esophageal disease?

*Dr. Kramer:*—That is a hard question to answer. I would estimate in about, 60 or 70 per cent.

*Dr. Ingelfinger:*—I should think it would be somewhat higher—possibly 10 or 15 per cent higher. On the basis of the duration of the dysphagia, its course, whether intermittent or steadily progressive, and the over all clinical picture, a good diagnostic guess should usually be possible. On the other hand, in some cases, and unfortunately this may be true of cancer, the esophageal disease may be fairly advanced by the time dysphagia first appears.

Now we will turn to the radiologist, and I will ask Dr. Schatzki to evaluate the accuracy of routine gastrointestinal x-ray examinations in diagnosing esophageal disease.

*Dr. Schatzki:*—Unless special diagnostic procedures are undertaken, some of the important diseases of the esophagus may be missed. Varices of the esophagus might be missed. You might miss small cancers, and you would miss, I think, probably the most common cause of dysphagia, that is the lower esophageal ring.

(Slide) You see what appears to be a perfectly normal esophagus. Now, this patient happened to have a lower esophageal ring, and if you distended the esophagus a little more, as shown here, you see the characteristic constriction at the lower end of the esophagus. In examining the esophagus you have to distend it and test its elasticity, because the absence of elasticity in any given cross-section of the esophagus is probably the most common cause of dysphagia.

I believe dysphagia is one of the most enjoyable clinical symptoms for the examiner, because when it is present you have the greatest chance to find the cause of the patient's complaint. I do not know of any other digestive symptoms where one is more likely to find the cause of the trouble, and you cannot afford to let the patient with dysphagia leave you without finding out its cause.

*Dr. Ingelfinger:*—May I ask one thing that bothers me: Why do radiologists use a capsule to test esophageal patency and function? It is wide one way and

small the other, and it thus might or might not stick in a narrow portion. Secondly, it is of such shape that esophageal peristalsis cannot grasp it very well, and it thus is held up even in a normal esophagus at times. If you really want to find the cause of dysphagia, you should not give a capsule, but the kind of food that normally sticks, as determined by history. If the patient says a meat sandwich sticks, give him a meat sandwich to swallow with the barium and not a capsule. This will show up the point of arrest dramatically.

Is this a wrong idea on my part?

*Dr. Schatzki:*—No. As we have discussed before, I think either way is all right. I think the capsule has both advantages and disadvantages. The advantages are that it has a certain diameter, and you have therewith a definite test diameter, which is readily available for testing.

I think the ideal object for testing esophageal patency would be a disc-shaped object. Since most obstructions are obstructions in all directions, it would be perfectly sufficient. A nice wide disc would be best—like a five-cent piece. Unfortunately, I haven't been able to get any of the drug manufacturers to make something of that shape that could be used.

*Dr. Ingelfinger:*—Dr. Soutter, would you mind discussing when esophagoscopy is indicated? Are there any particularly strong indications or contraindications?

*Dr. Soutter:*—I think the indications are when esophagoscopy is going to be very useful in establishing diagnosis, particularly by pathologic means. In cardiospasm in an older person, for example, you may be uncertain whether or not the patient has developed carcinoma. In a patient with esophagitis, the lesions may not show up radiologically, and the diagnosis can be established by esophagoscopy and biopsy.

Carcinoma is in a very special class and I have very strong feelings about it. If the carcinoma roentgenologically is quite clearly a carcinoma, and the patient is a reasonable surgical risk, and you intend to treat the case by surgery, esophagoscopy is unnecessary. The patient is saved thereby not only a procedure, but also what may be a dangerous procedure. The average patient with esophageal cancer is 65 years of age, and those in the older age group are more likely to get into trouble at esophagoscopy. I have seen several esophageal cancer patients esophagoscoped quite unnecessarily, who have developed perforations, and one or two have died or have been prevented from having surgery.

If, on the other hand, the diagnosis is uncertain prior to going ahead with major surgery, it is wise to esophagoscope the patient. Also, if you intend to make use of some other mode of therapy, such as x-ray treatment, initial diagnosis should in every case be established, to avoid treating something which looks like carcinoma but perhaps is not.

I think in patients with esophageal diverticulum, esophagoscopy can be very dangerous. It is easy to enter the sac and to perforate it. It is also very difficult to get the scope past a large diverticulum at the pharyngeoesophageal junction.

My general feeling about esophagoscopy is that it can be a dangerous procedure and should not be employed indiscriminately. The patients should be carefully chosen, and the doctor should decide whether it is really necessary.

*Dr. Ingelfinger:*—Dr. Kramer, would you discuss spasms of the esophagus? Is this merely a loosely used term, or does it refer to a definite clinical entity?

*Dr. Kramer:*—There is a condition called diffuse spasm of the esophagus. It is my impression that diffuse spasm has been called by a vast number of other names, such as spastic esophagus, pseudodiverticulosis, corkscrew esophagus, segmental esophagus, ladder spasm, nonsphincteric spasm, etc.

To me it is a definite clinical entity seen in the elderly individual. It occurs on swallowing and the patient has definite dysphagia. He also has pain. Now, this pain may occur on swallowing, or it may occur without swallowing. Diffuse spasm is to be distinguished from cardiospasm, for cardiospasm is not really spasm of the cardia, but a disorder involving most of the esophagus. Diffuse spasm is distinguished by the segmental contractions of the body of the esophagus, by the fact that the esophagus does not dilate, and by the fact that emptying is not impaired too greatly. What is confusing about diffuse spasm, however, is the fact that a similar radiological picture may be obtained in patients without any symptoms whatsoever. In these patients, usually elder people, the segmental spasms have been called tertiary contractions, or "Kräuselung", or curling.

*Dr. Ingelfinger:*—Dr. Schatzki, you introduced that word "Kräuselung". Will you elaborate on the significance of curling as you see it during ordinary x-ray examinations? I also think you once said that severe curling, diffuse spasm, or pseudodiverticulosis was, in your experience, not commonly associated with dysphagia. Since this experience is different from ours, will you give us your version of this?

*Dr. Schatzki:*—Curling is a very common affair, and, as Dr. Kramer indicated, at one moment is visible, when you see contractions of the esophagus, and the next moment you may look and the organ is completely normal in appearance, or we may see a few small diverticula. Curling is frequently associated with these diverticula.

I have seen total spasm of the lower two-thirds of the esophagus without curling, and I think that is what Dr. Kramer means. Occasionally patients with such total spasm have dysphagia, but I have not seen any symptom that is really connected with a picture of curling.

In my opinion curling does not produce occlusive spasm nor is it associated with dysphagia.

*Dr. Ingelfinger:*—(Slide) This slide shows what we call diffuse spasm, or rather, what the Mayo Clinic calls diffuse spasm. All these people had dysphagia. What do you call this, Dr. Schatzki?

*Dr. Schatzki:*—A severe degree of curling. I have seen a number of patients like these. I think if these patients have dysphagia, something additional is wrong.

*Dr. Ingelfinger:*—This is the one point where I want to disagree with you clearly because we think, without question, that diffuse spasm causes dysphagia.

*Dr. Kramer:*—We did a Mecholyl test in these patients, and those with definite dysphagia had a positive Mecholyl test in that their esophagus was highly sensitive to Mecholyl. It caused a tetanic spasm of the esophagus. This slide shows a positive Mecolyl test. You see first the control, a balloon kymograph tracing of esophageal motility. Then Mecholyl is injected, anywhere from 2 to 4 mg., and a contraction of the esophagus ensued, expelling all the air from the balloon. This does not occur in normal individuals.

Three of these patients given Mecholyl experienced pain which simulated the pain that they experienced on swallowing.

*Dr. Schatzki:*—I am highly interested in this observation, but I am wondering, since curling becomes visible with contraction of the esophagus, whether these patients for some reason had a contraction that brought out their curling. I still doubt that curling is by itself the cause of their symptoms.

*Dr. Ingelfinger:*—We have a question here: "Where did you get the information that inspiration increases abdominal pressure? I am quite sure that Dr. Cannon found the opposite years ago."

When the diaphragm descends on inspiration, it expands the thorax and squeezes the belly. This raises intraabdominal pressure and can be nicely shown not only in animals but also in human subjects, especially when they are lying supine. If a balloon record is obtained in the thoracic esophagus, the pressure within it drops when the patient breathes in, or if you measure intraluminal esophageal pressure directly, you discover this same phenomenon. It is as a matter of fact, a beautiful way of telling exactly where the thoracic and peritoneal cavities are separated in terms of the esophageal lumen. If a small catheter is placed in the stomach intragastric pressures rise as the patient breathes in. Then, if the catheter is withdrawn cm. by cm., it suddenly reaches a point, not more than 3 mm. in axial extent, where the direction of inspiratory pressure excursions suddenly changes and you obtain the increased negative inspiratory pressures characteristic of the thorax.

Dr. Schatzki, there have been several questions addressed to you, apparently related to what you said in studying the esophagus radiologically. Here is one: "How do you distend the esophagus during fluoroscopy?"

*Dr. Schatzki:*—In the upper part of the esophagus you let the patient swallow large or repeated boluses, but immediately above the diaphragm the easiest way to do it is to let the patient take a deep breath. At that moment the flow of barium through the hiatus is cut off, and with the sudden cut-off the lower end of the esophagus is distended. You can increase the distention if the patient does a Valsalva maneuver, but it is usually not necessary, for a deep inspiration as the barium approaches the diaphragm is sufficient to distend the lower end of the esophagus.

*Dr. Soutter:*—The first question I have is: "Cannot an epiphrenic diverticulum cause dysphagia, without obstruction of the esophagus?"

Of course it can. They lie directly in the pathway of swallowed food. They fill, and the food spills over. If they are very big, they will compress the distal esophagus so it is difficult for the food to go down it. On the other hand, before they get very big, and occasionally with the big ones, there is dysphagia but no actual obstruction of the esophagus.

The next question is: "Do you esophagoscope a patient during active bleeding from the upper gastrointestinal tract if the patient is in impending shock?"

My inclination would be not to do this, for two reasons. In the first place, it is dangerous, and I don't think you should esophagoscope a patient when it is very dangerous, unless there is something to be gained diagnostically or therapeutically. It is more difficult to see esophageal varices in the presence of blood, or it may be impossible; so it is less likely to be an effective procedure as it would if the esophagus were completely clean.

The second reason is that most upper gastrointestinal bleeding comes from the stomach rather than from esophageal varices.

The last question is: "What are your indications for surgery in achalasia; what is the technic used, and what are the results?"

I will answer as briefly as I can.

We consider that surgery should be conducted for achalasia if the patient has had a prolonged course which has not responded to any other form of therapy, or if we have a patient in whom the nutrition is severely affected, even though the disease has not been of long standing. The procedure should be the simplest which will be effective, and the simplest, as a starting point, is to pass a pneumatic bag, which can be pumped up to about the diameter of 4-5 cm. under 15 lbs. pressure. It is a little bit better than some of the metallic dilators in that it distributes pressure very well. If one of these is passed under fluoro-

scopic control and put in the exactly correct position—and that is a point well worthy of emphasis, for if it is too high or too low, it will not be effective—and then dilatation carried out, it will usually rupture the hypertrophied circular muscle, which seems to cause the difficulty. It is usually as effective as open surgery. It is something like the Heller operation in effect, but puts the patient through a great deal less trauma.

I do not believe dilatation with mercury bougies is an effective means of helping these individuals. All that happens is that the muscular fibers have been stretched a little bit, and relief is temporary. If forcible balloon distention is not effective, the next procedure to try is a Heller operation and, if that is not effective, we have to think of various plastic procedures. In our hands, however, we have had complete success in using the Mosher bag. I should ay in only one patient have we been only partially successful, and that was one in whom I did not get the bag positioned correctly.

*Dr. Ingelfinger:*—Here is a question addressed to Dr. Kramer: "Can you say something about *globus hystericus*?"

*Dr. Kramer:*—*Globus hystericus* is a sensation as if you had a lump in your throat. I can vouch for the fact that it can exist. Recently I had to make an important decision, and I felt this lump in my throat, associated with a marked anorexia. Although this sensation is present in the throat, it does not interfere with swallowing. Conversely, it is present in the absence of swallowing.

*Dr. Ingelfinger:*—We will end with this important question: "How do you make the diagnosis of diaphragmatic hiatus hernia associated with esophagitis?"

*Dr. Schatzki:*—(Slide) The diagnosis of hiatus hernia at times is very easy. In this slide, the diagnosis is very obvious. Unfortunately, these are not the cases you usually see. You usually see cases like these (slide) and the diagnosis is extremely difficult. One reliable evidence, I find, is demonstration of the intrinsic sphincter of the lower end of the esophagus, about which I spoke before, but this is not so easy at times. There are similar constrictions within the esophagus at times which are difficult to differentiate from those at the lower end of the esophagus.

For a long time we have been seeking a landmark which would be reliable. Folds are not reliable; the sphincter may be reliable if seen, but I think we finally have one that is reliable and that is the lower esophageal ring. We have suspected for some time that this was the borderline of the esophagus and stomach, and I think we have proven it.

*Dr. Ingelfinger:*—Under what definition? What joins there, the muscle?

*Dr. Schatzki:*—I do not know. Certainly esophageal and gastric mucosa meet there. Dr. MacMahon says the ring is primarily caused by duplication of

mucosa and that it contains *muscularis mucosae* but not the musculature of the esophageal wall.

*Dr. Ingelfinger:*—Then it is not contractile?

*Dr. Schatzki:*—I didn't say that.

*Dr. Ingelfinger:*—Well, I would say so. I think Dr. Kramer and I retreat from the position that the lower esophageal ring is principally a muscular phenomenon, but I still don't think it helps us determine where the esophagus ends and the stomach begins.

There are many, many questions here that we have not been able to ask, but we can't impose on you any longer.

Thank you very much.

# DUODENAL ULCER IN CHILDREN*

JOSEPH SHAIKEN, M.D., F.A.C.G.†

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## Introduction

Duodenal ulcer has been generally recognized as a disease occurring in adults and particularly in the adult white male in whom it represents the most frequent organic disease of the upper digestive tract.

The diagnosis of duodenal ulcer in children has been given considerably less general acceptance. A good deal of hesitancy, resistance and even skepticism has been noted among some pediatricians, general practitioners and others when a diagnosis of duodenal ulcer has been suggested as a cause of recurring abdominal pain in children.

Abdominal pain is one of the most common childhood complaints[2]. It is the presenting symptom in a long list of intraabdominal diseases. As in the adult, abdominal pain of psychogenic origin is more frequent than abdominal pain due to organic disease. These observations, however, must not obscure the fact that duodenal ulcer not infrequently is a cause of recurring abdominal pain in children.

## Incidence

It is difficult to determine accurately the number of children who have duodenal ulcer.

The world literature contains about 500 cases of gastric and duodenal ulcer in children[4]. This represents but a small fraction of the total number of children with this disease. Duodenal ulcer was 3-7 times as frequent as gastric ulcer[4].

In one report of a study of peptic ulcer in children[7] 80 patients were found in 12 years of practice. A family history was noted in 9 patients. The youngest patient was 4 years of age, the oldest 14 years of age. Boys predominated in a proportion of 8 to 1.

In another report[6] 45 children with peptic ulcer were diagnosed in one children's hospital in one year. The children ranged from 1 to 11 years of age.

In another study[1] in a general hospital and in private practice 30 children with peptic ulcer were found in a gastrointestinal x-ray study of 254 children.

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In my own experience 109 children with abdominal pain were examined by x-ray study of the gastrointestinal tract. Although the majority of the children had no organic disease, 23 peptic ulcers were found, 18 of these were duodenal ulcers and 5 gastric. Duodenal ulcer was the most frequent cause of organic disease in this group.

In obtaining a history from an adult patient with duodenal ulcer it is not uncommon to obtain a typical history of duodenal ulcer which apparently started in childhood. Occasionally the diagnosis was established by appropriate x-ray studies or in others surgery was done for complications. The exact number of adult patients whose history dates back to childhood has not been determined but such a study would be useful.

What is the significance of a family history of peptic ulcer?

In the group studied there were two patients with parents each of whom had a duodenal ulcer and six in whom either the mother or the father had a a duodenal ulcer. There were two pairs of brothers with duodenal ulcer.

Any child with recurring abdominal pain deserves a gastrointestinal x-ray study but particularly so if there is a family history of peptic ulcer.

## Etiology

In the adult some attention has been paid to the significance of emotional factors in peptic ulcer, in children considerably less attention has been given to these factors[3].

In children unpleasant family relationships, difficulties with playmates, unpleasant situations at school and other real or imaginary difficulties create a great deal of worry, tension and mental strain which may be of etiological significance in the development of peptic ulcer.

It has been noted that the children with duodenal ulcer are high strung and nervous[5]. Emotionally, as in the adult, the children have a strong need for love and affection, a need for praise and appreciation[3]. The children are well behaved, tense and anxious. Their need for love and affection is striking. They are constantly anxious to secure approval and affection in every area of their lives[3]. Their need for affection is so limitless that the superficial reassurances they receive in everyday situations cannot relieve their anxiety. In general these observations in children with peptic ulcer are quite similar to those described in adults with peptic ulcer[3].

## Classification

Peptic ulcer in children has been classified as follows[8]:

1. Peptic ulcer of the newborn.

2. Peptic ulcer of the young infant.

3. Peptic ulcer in children 1-9 years of age.

4. Peptic ulcer in older children.

My experience has been limited to the two last groups. The information obtained from the reports of others and my own experience would suggest a classification of these two groups as follows:

1. Peptic ulcer in the young child.

2. Peptic ulcer in the teen-age group.

This division has suggested itself as a natural one because of the difference in symptomatology, x-ray findings and response to treatment in these two groups.

The very young child with peptic ulcer generally has abdominal pain which may be periumbilical or epigastric in origin. Sometimes the pain is generalized. Gastric distress may be manifested by nausea and vomiting. The abdominal complaints are not usually related to food intake, and the sequence of pain with food relief is not generally found. The pain is usually more severe in the morning and is often initiated by trying to eat breakfast. Sometimes vomiting occurs after a few bites of food are taken. This usually gives relief of distress. Vomiting is not frequent, but nausea is common. The one constant symptom is abdominal pain.

In the teen-age child the symptoms are more of the type one encounters in the adult with ulcer. The food-comfort-pain sequence is common. The typical history of recurring abdominal pain brought on by hunger and relieved by food intake may be elicited by direct questioning. These children eat a great deal and often, because they have found that food gives them relief of distress. They usually eat or drink frequently and thus may not realize that the distress which they are experiencing is anything but a feeling of ordinary hunger. Many children will continue this way until a hemorrhage, repeated vomiting or more severe distress will suggest that medical care is urgently needed.

## Diagnosis

The observation was made nearly 25 years ago that the most important single factor in the diagnosis of peptic ulcer in children is the realization that chronic peptic ulcer occurs in children[10].

Regardless of the age of the child a complaint of epigastric pain occurring sometime after meals and particularly at night, relieved by milk or other food or vomiting, accompanied by tenderness in the upper right portion of the abdomen should lead to a very strong suspicion of peptic ulcer and should be an indication for a roentgenologic examination of the stomach and duodenum.

## Radiology

As in the adult the diagnosis of duodenal ulcer in children is made by a fluoroscopic and x-ray examination[9]. The examination is similar to that in the adult. It is sometimes more difficult to do. Flavoring the barium sulfate, the use of "straws", putting the barium mixture into a malted milk may help the young patient to take the required amount necessary for examination. The presence of pylorospasm or the presence of gastric retention makes the examination difficult at times[9].

The roentgen study of the younger child seldom reveals the presence of a deep ulcer crater as seen in the adult patient. In the teen-ager the typical ulcer crater noted in the adult patient with active duodenal ulcer is not an unusual finding.

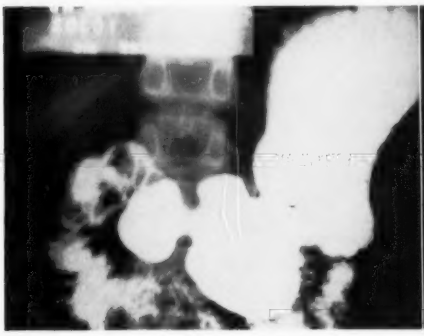

Fig. 1

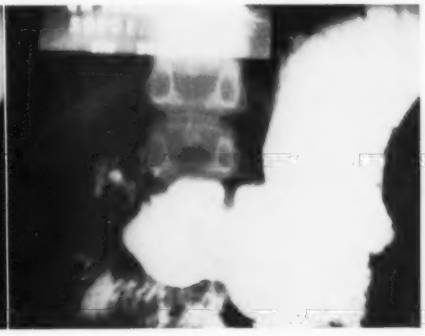

Fig. 2

## Differential Diagnosis

In the differential diagnosis one must consider mesenteric adenitis, appendicitis, volvulus, intussusception, acute pyelonephritis as well as psychogenic abdominal pain.

## Treatment

The treatment of the child with a duodenal ulcer differs very little from that of the adult.

The diet is a typical multiple feeding program with a liberal use of easily digested foods. Milk is usually well tolerated. Meat and meat products and other sources of protein are important in the growing child and are useful.

The usual antispasmodics, antacids, bowel aids and sedatives are prescribed.

Discussion of the ulcer problem involved should be very elementary with the young child. Children listen a lot, hear a lot and many of them have a vivid

imagination. The term "stomach ulcer" brings to them strange and fearful notions as to the seriousness of their condition and may interfere with treatment.

The teen-age child has to be told what the disease is. Why he must not smoke. Why he must adhere to a diet. The ultimate good result of treatment must be emphasized.

It is important to remember that the child must be treated not only for the disturbed upper gastrointestinal tract but for the disturbed personality and emotional problems which are usually present.

Formal psychiatric treatment has seldom been necessary.

## Prognosis

In general the prognosis is good. Four children out of 18 had hemorrhages. The hemorrhages were not severe and responded quickly to blood replacement, diet and sedation.

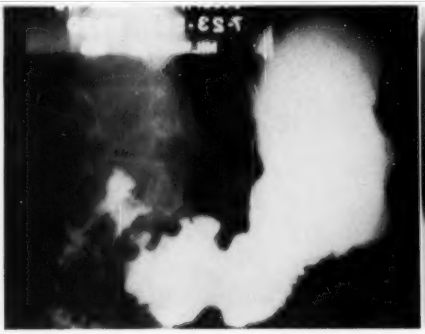

Fig. 3

Fig. 4

Two patients eventually were treated surgically. One because of hemorrhage and obstructive symptoms, the second because of recurring pain and failure to respond to medical treatment.

Although some of these children with duodenal ulcer will continue into adulthood with recurring attacks of ulcer activity—in general the greater number respond well to medical treatment and have no further trouble.

## Review of Patients

1. A white male, age 14, developed distress in the abdomen in the late afternoon and was wakened at night with distress. The patient's mother had gallstones and a duodenal ulcer. Roentgen studies revealed a large duodenal ulcer crater. The response to an ulcer regime was good (Figs. 1 and 2).

2. A 16-year old white male developed distress each day in the mid-morning. Roentgen studies disclosed a typical adult type duodenal ulcer with a crater. Response to medical treatment was only fair. Later this patient developed a hemorrhage which responded to medical treatment. The ulcer symptoms have never completely subsided, because the patient has been very uncooperative and difficult to manage (Fig. 3).

3. A white male, age 17, complained of gas pains and constipation for several months. He was very nervous and very tense. He worried a great deal about himself. He was moody and at times severely depressed. The x-ray studies revealed an active duodenal ulcer with a crater and a deformed duodenal bulb. His response to medical treatment was poor (Fig. 4).

4. A white boy, age 10, developed abdominal pain relieved by eating. The child was very tense and nervous. He was a good student. X-ray studies revealed a duodenal ulcer. The response to medical treatment was good (Fig. 5).

Fig. 5

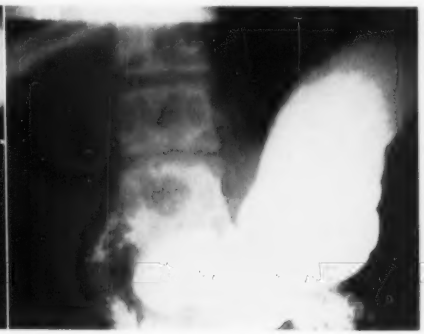

Fig. 6

5. A child, age 5½, developed stomachache, nausea and vomiting. X-ray studies revealed a duodenal ulcer. The medical treatment relieved the symptoms promptly (Fig. 6).

6. A white male, age 18, complained of cramps for one year. He had heartburn frequently. He began to pass tarry stools, felt weak and fainted. The examination revealed a pallorous but well nourished young man. The studies of the upper digestive tract revealed a typical duodenal ulcer. A medical program for duodenal ulcer was started. The response to medical treatment was good. Repeat x-ray studies of the stomach and duodenum revealed a deformed duodenal bulb.

7. A white female child, age 8½ years, had abdominal pain for months. The child was bright, tense and well behaved. The roentgen studies revealed a duodenal ulcer. Medical therapy relieved the symptoms promptly.

8. A white 14-year old boy, had severe abdominal cramps. Food relieved the distress. A study of the upper digestive tract revealed a typical adult type duodenal ulcer with crater. The response to medical treatment was fair. The boy was very tense and an excellent student. Subsequently he had a hemorrhage from the ulcer which responded to medical treatment.

9. A 16-year old white male complained of abdominal distress, cramps and night pain. The roentgen studies revealed an active duodenal ulcer with crater formation. The response to medical treatment was fair. Recurrences were frequent. A hemorrhage occurred. Later obstructive symptoms developed which necessitated a subtotal gastrectomy.

10. A white female child, age 10, developed pains in the abdomen and severe constipation. Roentgen studies revealed a duodenal ulcer. The response to medical treatment was very good. This child was an excellent student.

## Summary

In a child who complains of recurring abdominal pain duodenal ulcer should be high on the list of possible causes. A fluoroscopic and x-ray study of the digestive tract is essential in making the diagnosis.

The response to medical treatment is usually satisfactory.

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## Discussion

*Dr. I. R. Jankelson (Boston, Mass.):*—I first became interested in this problem some 30 years ago, when a pathologist showed me a specimen of a duodenal ulcer in a stillborn infant. I have since then studied this problem intermittently and reported my findings on it.

Actually the diagnosis of peptic ulcer in children is practically in the state in which the diagnosis of peptic ulcer, whether gastric or duodenal, was in adults about 35 or 40 years ago.

The vast majority of the cases which are diagnosed are not because an ulcer is present but because one of the important complications has developed, such as pyloric obstruction, hemorrhage, or perforation. Only then does the physician think of the possibility of an ulcer; in other words, we have to educate the pediatrician to look for ulcers.

*Dr. C. Wilmer Wirts (Philadelphia, Pa.):*—I should like to ask Dr. Shaiken when the x-ray examinations are carried out in a rather small child, should any special precaution be taken to avoid undue hazard?

*Dr. H. B. Eisenstadt (Port Arthur, Texas):*—I think that one of the main reasons for the scarcity of ulcer diagnosis in children is the technical difficulty of the x-ray examination. I have been using Dibuline (Dubutoline-Merck) 1-3 c.c. subcutaneously as a very effective, very fast relaxing anticholinergic during my x-ray examinations. It will abolish spasms, abnormal peristalsis, and other functional changes within a few minutes and make it possible to demonstrate ulcer deformity and niche which otherwise cannot be visualized with even the fastest x-ray machinery. We should not be mislead to make the diagnosis of ulcer on the basis of functional changes alone especially in children.

*Dr. John M. McMahon (Bessemer, Ala.):*—I hate to keep bringing up the cultural aspects of disease, but in our section of the country, when children come in with recurrent abdominal pain, it turns out that 99 out of a hundred have worms.

*Dr. Joseph Shaiken (Milwaukee, Wisc.):*—First of all, you might be interested to know why I presented this subject at this time. The current journals on gastroenterology have not published any discussion on peptic ulcer in children in many years.

There was one paper in the *American Journal of Digestive Diseases* some 20 years ago. Since then, the papers I have reviewed, which have numbered about 35, have appeared in state medical journals or in the journals of small groups, not at any national level, and I felt it necessary that at least the gastroenterologist should be reminded that duodenal ulcer does occur in children.

Now, to answer some of the questions. We limit the fluoroscopy in these children and depend a good deal on film studies.

Regarding the difficulty with pylorospasm, these children do have a considerable amount of pylorospasm. If we take the child and spend a little time getting acquainted and winning the child's confidence, the difficulty is not serious. Occasionally the child is permitted to sit down for awhile, and we tell him exactly what we are going to do, and when we turn on the fluoroscope, many of the children behave very well.

We do not use anticholinergic agents in the treatment of these children. We have used tincture of belladonna and phenobarbital, alone or in combination and the results have been satisfactory.

Of the 18 patients I saw, two of them came to surgery. One because of hemorrhage and obstruction, and the other because of intractability.

Observations have been made that surgery is necessary in a high percentage of these children. I do not agree with these statements. There are several papers in which it is said that surgery is considered good treatment. I feel that these children can be handled adequately medically and respond well to medical treatment if you treat the whole individual and not just give the child a diet and a prescription. The emotional and nervous problems have to be considered in treatment. The situation at home and in school may need improvement and the family must help and understand what we are trying to accomplish.

# AN ADJUNCT TO DIAGNOSIS OF THE ACUTE PERFORATION OF THE UPPER GASTROINTESTINAL TRACT

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and

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In the examination of the acute surgical abdomen, the scout films have become a routine procedure in the establishment of a diagnosis. Air under the right leaf of the diaphragm is an important finding. An intensified search for this sign must always be made.

We are reporting an adjunct for diagnosis of the acute perforated viscus. There are several conditions in which air is present under the diaphragm. These are:

1. Perforation in the gastrointestinal tract.
2. *Pneumatosis cystoides intestinales humanis.*
3. Recent laparotomy.
4. Recent insufflation of the fallopian tubes.
5. Recent presacral insufflation.
6. Gas forming infection of the gastrointestinal and biliary tracts.

Free air under the diaphragm signifies a perforated hollow viscus except when conditions 2, 3, 4, 5 and 6 are present. In the present series free air has been demonstrated by x-ray in only 65 per cent of cases of perforated viscus. A review of the literature confirms this finding. This figure could be increased to 100 per cent by the suggested procedure.

When a patient is admitted to the hospital with a history of sudden onset of abdominal pain, a scout film is taken, and examination of the x-ray for free air under the diaphragm is made. If the latter is negative, and a perforation of the upper gastrointestinal tract is still suspected, the following test is done while the patient is still on the x-ray table:

A Levin tube is passed into the stomach and 200-300 c.c. of air is insufflated. The tube is clamped; the patient is gently rolled from side to side. After an interval of 10-15 minutes, flat and upright x-rays are taken. As a result of these

From the Surgical Service of the Coney Island Hospital, John E. Hammett, M.D., F.A.C.S., Director.

studies of 30 perforated peptic ulcers, 20 showed free air under the diaphragm in the original scout films and 10 were negative for free air. After insufflation of 300 c.c. of air in the latter 10 cases which were negative, however, free air was demonstrated under the diaphragm in all. This procedure has been found especially valuable as a diagnostic aid in a group of cases where abdominal findings are very frequently masked. This group includes the very old, the female who has had many pregnancies with a resultant lax abdominal wall, and uncooperative and emotionally disturbed patients.

At the time of operation the localization of the perforation is more readily found if the surgeon compresses the insufflated stomach, thus expelling air

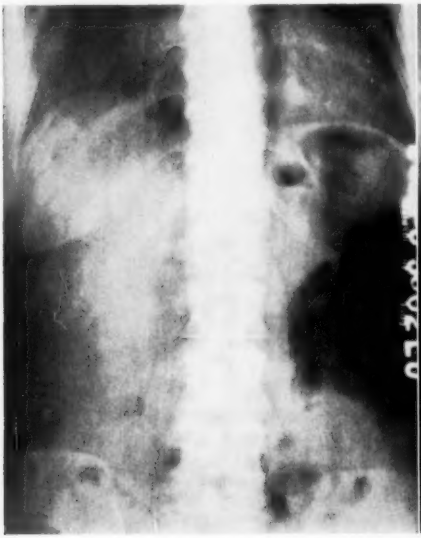

Fig. 1

Fig. 2

bubbles through the perforation. This is especially helpful in cases of perforation of the posterior wall of the stomach. This obviates extensive search for the perforation. The test is valuable in the diagnosis of the nonurgent surgical abdomen. Included in this group are impacted stones in the cystic duct and acute pancreatitis. Although these conditions produce a surgical abdomen, a negative test gives the surgeon additional time to improve the patient's condition.

The test is also valuable in a negative way, such as in tabetic crises, porphorynuria, myocardial infarction, pleurodynia, pneumonia, renal calculus, and other nonsurgical abdomens. The absolute indication for this procedure is in the patient in whom a fresh perforation is suspected and who is a candidate

for immediate surgery. The test is not done in patients in whom an old sealed-off perforation is suspected or in patients with a fresh perforation whose condition is such that surgery is not warranted. Three cases of perforation of the upper gastrointestinal tract are reported. These cases did not demonstrate free air under the diaphragm. After using this procedure, however, free air was demonstrated under the right leaf of the diaphragm.

These are cases of perforated peptic ulcer. Each case illustrates different reasons for negative free air under the diaphragm in the scout film. Free air, however, was demonstrated after insufflation.

*Case 1:*—A 15-year old white male was admitted to the Coney Island Hospital because of sudden onset of acute epigastric pain of 3 hours' duration. There was no history of an ulcer. Patient states that while he was performing athletics (chinning), he experienced a sudden epigastric pain. This caused him to double

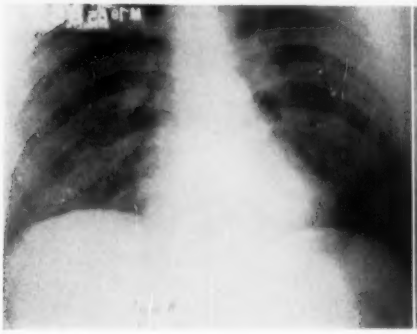

Fig. 3

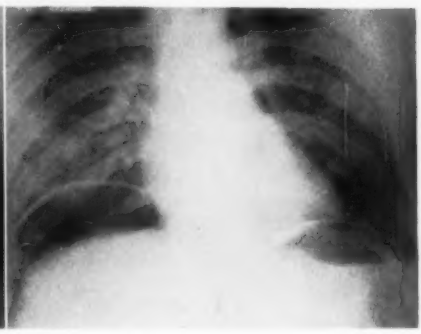

Fig. 4

up. He was not able to walk. On physical examination there was no radiation of the pain. Nausea and vomiting were present. Physical examination revealed a young adult male in acute distress. Temperature 99.8°, pulse 100, B.P. 110/60. He was pale and dyspneic. The abdomen had a board-like rigidity. There was no discoloration of the abdominal skin. No urinary findings. WBC, 9,900. Differential: polys. 70 per cent, lymphs. 28 per cent, monos. 1 per cent, eos. 1 per cent. Hb. 14 gm., BUN 10 mg. per cent, B.S. 120 mg. per cent, serum amylase 80 Smorygi units. Scout film was negative for free air under the diaphragm (Fig. 1). The clinical impression was "rupture of muscle fibres of the abdominal wall". A Levin tube was passed and 200 c.c. of air was injected. The patient was rolled from side to side gently. After a 15-minute interval an x-ray of the abdomen in the upright position was taken. Free air was demonstrated (Fig. 2). The clinical impression of ruptured viscus was made. Immediate surgery was performed. At operation a pin point perforation of an ulcer was found on the anterior wall

of the first portion of the duodenum. The perforation was closed and patient was discharged 12 days later.

*Case 2:*—A 45-year old white male was admitted for sudden onset of acute abdominal pain. The pain was of 2 hours' duration. There was no history of a peptic ulcer, hypertension, gallbladder disease, or previous surgery. On physical examination we observed an acutely ill patient. He was pale and dyspneic. Temperature 100°, pulse 100, B.P. 140/80. The pertinent physical findings were in the abdominal examination. There was generalized tenderness of the abdomen. Rigidity of both recti was present. There was rebound tenderness. Laboratory studies: WBC 7,800. Differential: polys. 75 per cent, lymphs. 20 per cent, monos. 3 per cent, baso. 1 per cent, eos. 1 per cent, Hb. 12 gm., B.S. 135 mg. per cent. Serum amylase 65 Smorygi units. BUN 14 mg. per cent. An upright and flat plate x-ray study of the abdomen were negative for free air (Fig. 3). The Levin tube was inserted in the stomach. Two hundred c.c. of air was insufflated.

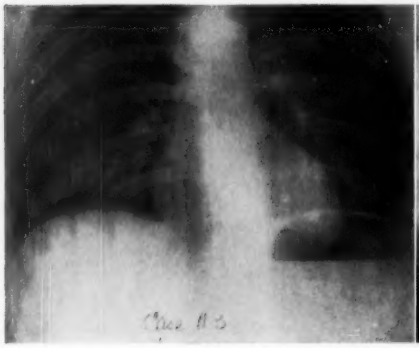

Fig. 5

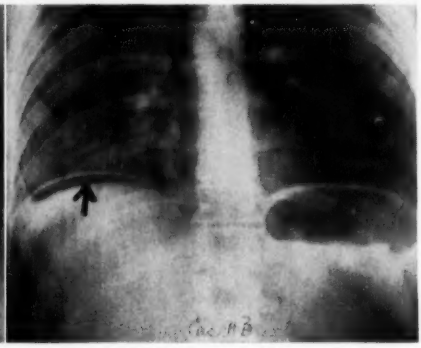

Fig. 6

The tube was clamped. Patient was rotated from side to side. Another upright film was taken. The latter showed free air under the right diaphragm (Fig. 4). The clinical impression of ruptured viscus was made. Immediate surgery was performed. A duodenal ulcer on the anterolateral wall of the first portion was found. A subtotal gastrectomy was performed. Patient made uneventful recovery, and was discharged on the 13th hospital day.

*Case 3:*—A 75-year old white male was admitted to the Coney Island Hospital because of generalized abdominal pain. The pain had commenced 24 hours prior to admission. Family informed the admitting physician that patient had been subject to indigestion for several years. An adequate history was not obtainable because the patient was mentally confused. Physical examination revealed: temperature 100.8°, B.P. 180/90, WBC 10,500, Hb. 11 gm. BUN 32 mg. per cent. B.S. 175 mg. per cent. Differential: polys. 80 per cent, lymphs. 15 per

cent, monos. 4 per cent, eos. 1 per cent, serum amylase 220 Smorgyi units. Examination showed slightly distended abdomen. There was moderate tenderness to palpation in the lower portion. There was no localized rigidity. Flat and upright film of the abdomen were negative for free air. A Levin tube was passed and 200 c.c. of air was insufflated. X-ray studies demonstrated free air under the right diaphragm (Fig. 5). Immediate surgery was performed. Examination of the stomach and duodenum did not reveal any perforation. Upon compression of the inflated stomach, however, air bubbles were seen to be expelled from the posterior wall of the stomach. A perforated postgastric ulcer was then visualized (Fig. 6). It was treated with a simple closure. The patient did well postoperatively and was discharged three weeks later.

## Summary

The procedure of insufflation of air in the stomach and follow-up with x-ray of the abdomen is a valuable adjunct to the diagnosis of the acute surgical abdomen. The indication for performance of this test is in the patient who has a fresh perforation and who is an immediate candidate for surgery and in whom scout films fail to reveal free air under the diaphragm.

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# THE USE OF SMALL MAGNETS TO LOCATE THE TIPS OF TUBES IN THE GASTROINTESTINAL TRACT WITHOUT FLUOROSCOPY

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Intubation procedures have been used in the study of alimentary tract function and disease for many years. Tubes made of rubber or plastic are used to obtain intestinal tract contents for chemical, microscopic and bacteriological examination, and to record intraluminal pressure changes. In the management of bleeding from the upper intestinal tract, a weighted string is often passed in addition to aspirating tubes[1]. In many of these procedures fluoroscopy is routinely performed to determine the location of the tubes.

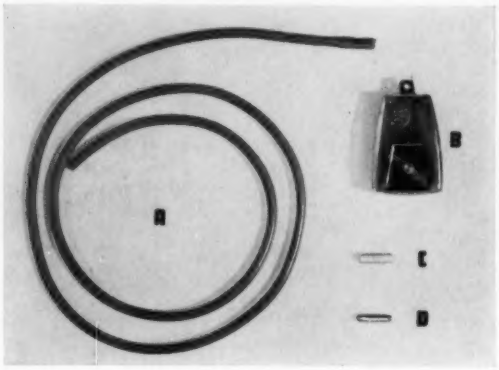


Fig. 1

Fig. 1. a—Magnet inserted into the end of #18 French aspirating tube.
b—Dresden Manuf. Co. "Stud-Finder".
c—"Magic Magnet" as received from Magnet Sales Company, ready for insertion into end of aspirating tube.
d—"Magic Magnet" made smooth on carborundum wheel, and grooved to facilitate tying onto string for Einhorn String Test.

The advisability of limiting radiation exposure to patients and medical personnel to an absolute minimum has been emphasized during recent years[2]. We therefore investigated the possibility of using a small permanent magnet and carpenter's magnetic "stud-finder" to locate the ends of ingested tubes and strings. By placing magnets at the distal ends of the tubes and strings, and monitoring the abdominal wall with a stud-finder we frequently located the

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tubes without resort to fluoroscopy. Our experience with this method in a series of intubations of the stomach, duodenum and jejunum is herewith reported.

## Method

*Subjects:*—Intubations with aspirating tubes were performed in 21 male patients, and string tests for occult or gross blood were performed in 3 others. All of the patients had been given x-ray examinations of the upper gastrointestinal tract prior to these studies.

*Equipment (Fig. 1):*—The magnets used were 2/16 x 3/16 x 7/8 inch rectangular bars with approximately 8 ounce pull, sold by the Magnet Sales Company* as #20 flat "Magic Magnets". The magnets fit tightly into the #18 Fr. tubes used for intubation at this hospital, and did not require machining of any

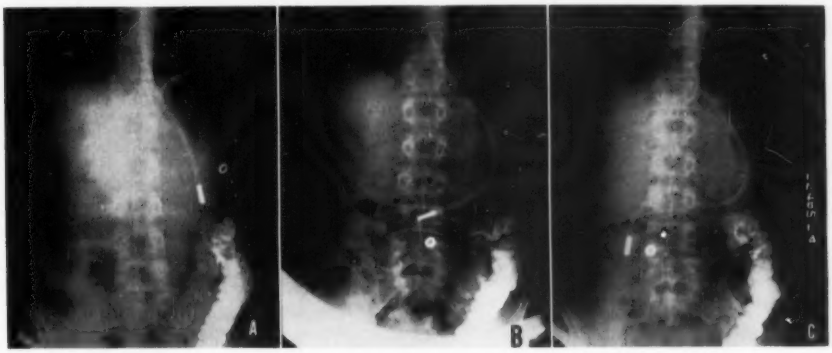


Fig. 2a Fig. 2b Fig. 2c

Figs. 2a, b and c—Serial films taken during the passage of a tube prior to biliary drainage. Marker "O" indicates position on skin of abdomen where stud-finder bar spun or deflected sharply. Fig. 2a, bile was aspirated from the tube at the time when the finder showed movement of the tip to the right of the midline (Fig. 2c).

kind. The magnets used as weights in the string tests were first ground smooth on a dental carborundum wheel, with care taken to heat or jar them as little as possible. The stud-finders used were manufactured by the Dresden Manufacturing Company†. The cost of 20 magnets and two stud-finders was four dollars. Both the magnets and the indicators in the Dresden Company stud-finders were made of "Alnico-Five", a permanent magnetic alloy.

When not in use, the equipment was stored in small cotton-padded cardboard boxes. Special care was taken to prevent direct contact between the magnets, stud-finders, and other magnetic objects. Care was also taken to prevent

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jarring during use. To date we have used some magnets 2 to 3 times a week for four months, without noting impairment of their effectiveness.

While the stud-finder was in use, care was taken to see that no metal objects (belt-buckles, buttons, etc.) were in the area surveyed.

*Gastric intubation:*—Gastric intubation was performed by having the patient swallow the rubber tube until the magnet at its tip was 50 cm. from his incisor teeth. The stud-finder was then passed back and forth over the skin of the abdomen. The stud-finder was held next to the skin, with the plastic face visible to the examiner. When the stud-finder passed over the ingested magnet, its bar usually reacted by spinning or suddenly deflecting sharply. Movement of the bar while the stud-finder was held over the umbilical or left lumbar area was interpreted as showing that the tube tip was in the body or antrum of the stomach.

Fig. 3a Fig. 3b Fig. 3c

Fig. 3a—Intubation of gastric pouch in a patient with suspected marginal ulcer. Marker "O" indicates site of reaction by stud-finder bar. Tube was withdrawn 1 inch and aspiration for acid performed.

Fig. 3b—Jejunal intubation in the same patient. "O" marker shows site of stud-finder bar movement in the left iliac area.

Fig. 3c—Gastric pouch intubation in another subject. Marker shows where the stud-finder bar reacted to the underlying magnet.

When no movement of the bar occurred, it was assumed that the tube tip was above the costal margin, and an additional 10 cm. of tube was slowly passed. This usually moved the tip into the body of the stomach. In cases where a bar deflection could not be elicited after passage of 60 cm. of tube, it was assumed that the tube had coiled and that the magnet was in the fundus, above the costal margin. When this occurred, the tube was withdrawn until the tip was 40 cm. from the incisor teeth, then re-passed in 10 cm. increments while the stud-finder monitored the anterior abdominal wall.

*Duodenal intubation:*—Duodenal intubation was performed by passing the tube until the tip was 40 cm. from the incisor teeth. The patient was then turned onto his right side, and the tube was passed an additional 20 cm. The stud-

finder was used to locate the tip of the tube. When the stud-finder showed that the tube tip was in the umbilical area, the tube was slowly advanced during the next hour until the stud-finder showed that the tip had moved to the right side of the abdomen and downward. This was interpreted as evidence that successful duodenal intubation had been performed. When the tip could not be located by the stud-finder, the patient was asked to sit up, and the abdomen was again monitored. When this maneuver also failed to produce a deflection of the stud-finder bar, it was assumed that the tip was in the fundus. The tube was then withdrawn until it was 40 cm. from the incisor teeth, the patient resumed his position on his right side, and the tube was again passed to 60 cm.

*Gastric pouch intubation:*—The tube was passed until the tip was 40 cm. distal to the incisor teeth. The stud-finder was then passed back and forth over the left upper quadrant while the tube was slowly advanced further. The stud-finder bar usually deflected as soon as the magnet in the tube passed below the costal margin. This was interpreted as evidence of successful gastric pouch intubation. The patient was then asked to lie upon his back, and the aspiration for free acid or blood was performed. On those occasions when the stud-finder indicator moved when passed over the left iliac area, it was assumed that inadvertent jejunal intubation has been performed, and the tube was pulled back until the stud-finder showed the tip to be in the left upper quadrant of the abdomen.

*The Einhorn string test:*—One of the machined Alnico magnets was tied to a piece of string 80 cm. in length. The patient was asked to swallow the magnet before retiring, and the end of the string was taped to his cheek. During the night the string was slowly ingested. The following morning the stud-finder was used at the bedside to determine how far into the gastrointestinal tract the string had advanced. It was assumed that the end of the string was in the duodenum when the needle deflected over the right side of the abdomen adjacent to or below the umbilicus. The string was then removed, and examined for blood stains and bile. In subjects who had had subtotal gastrectomy, movement of the stud-finder bar when it was held over the left ileal region was interpreted as indicating that the end of the string was in the jejunum.

## Results

*Accuracy:*—In 19 of the 24 patients tested, the stud-finder bar moved as the instrument was passed over the abdomen. A lead marker was placed on the skin at the site where the stud-finder bar deflected, and immediate x-rays were taken. As the tubes were passed further into the intestinal tract repeat films were taken, and a total of 40 films were obtained. These films showed the ingested magnets to be within 1½ inches of the skin markers (Figs. 2 and 3). The stud-finder bar did not move when used to locate magnets swallowed by the other 5 patients. In two cases, the x-ray films showed the tube tips to be in the distal esophagus

or fundus of the stomach, above the costal margin. In the other 3, the x-rays showed the tube tips to be in the body of the stomach, well below the costal margin. These patients had very thick abdominal walls, two because of exceptionally well developed musculature, and one because of marked obesity.

In the 19 patients in whom the stud-finder showed the quadrant in which the ingested magnet was located, reference to previous barium meal studies made it possible for us to decide whether the magnets were in the stomach, duodenum, or jejunum. This was *usually* confirmed by the nature of the aspirate obtained, and the location of bile stains on the strings.

*Artifacts:*—Sudden movements by the patient or the examiner's hand caused the stud-finder bar to deflect. These deflections did not re-occur when the stud-finder was passed back and forth over the area in question, and did not constitute a serious problem.

*The effect of the stud-finder on the ingested magnets:*—On several occasions the stud-finder was passed back and forth over the ingested magnets, under fluoroscopic guidance. No movement of the underlying magnets was noted, either toward or away from the magnetic indicator in the finder.

*Adverse effects:*—The patients did not object to swallowing the small magnets, and often expressed great interest in the stud-finder and its indicator. No untoward reactions of any kind occurred during this investigation.

## Comments

Alnico-Five magnets first became available during World War II. Since then several technics for facilitating duodenal intubation by using these magnets in conjunction with fluoroscopy have been described[3,4]. Alnico-Five is a relatively noncorrosive metal which is no more harmful, when ingested, than any other nonabsorbable substance of similar size and shape. Because of their peculiar properties[5] magnets have, in fact, been used in some therapeutic programs[6,7]. Children have been fed small magnets, in the hope that previously ingested sharp metal objects would cling to them, and magnets have remained in the alimentary tracts of children for over 24 hours without demonstrable ill effects[6]. Perforation of the stomach by ingested nails and pieces of barbed wire occurs frequently in cows. The introduction of Alnico magnets into the animals' stomachs, where they serve as anchors for other ingested magnetic substances, has helped farmers deal with this problem[7].

The method described in this paper does not use magnetic forces large enough to pull tubes along the intestinal tract, and does not use magnets as therapeutic agents. The method does, however, use the effect of one magnet upon another to provide a safe, convenient bedside means of locating the tips of tubes passed into the intestine. We therefore feel that this method will be helpful in all cases in which an orally-passed tube with distal weight is used in

diagnostic procedures, and recommend it as a technic which will frequently eliminate the necessity of using x-ray equipment.

## Summary and Conclusion

A simple, safe, and inexpensive method for locating the ends of aspirating tubes in the upper gastrointestinal tract has been described. The method is based upon the reaction of the indicator needle of a carpenter's stud-finder to the presence of another Alnico-Five magnet, and achieves its purpose without need for fluoroscopy.

## Acknowledgment

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# THE GASTROENTEROLOGICAL ASPECTS OF PERIARTERITIS NODOSA*

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*Periarteritis nodosa* was described in the literature in 1866 when Kussmaul and Maier first reported and named a new disease characterized by multiple degenerative lesions of the small arteries. The unusual and varied clinical manifestations in association with an often bizarre peripheral blood study enabled the diagnosis to be made only infrequently. This entity, however, remained a favorite of pathologists who collected slides of exotic diseases and of clinicians who conjectured upon the etiology of this disorder. Since that time the frequency of articles appearing on this subject has multiplied greatly. Johnsson and Leonhardt[1], remark in their study that more than 750 cases were on record by 1954. It is of course, necessary to note that many unreported cases have been discussed in conferences and demonstrated by pathologists.

*Periarteritis nodosa* can no longer be considered a rare disease. It is on the increase and had received more attention in the last two decades because of two outstanding reasons. Rich's[2] important contribution relating the association of hypersensitivity and *periarteritis nodosa* has stimulated great interest. Many investigators have experimentally produced lesions similar to those seen in the disease. Zeek[3], in an excellent review of this subject, states that in recent years *periarteritis nodosa* has come to include not only the type of lesions originally described under that name, but in addition many other vascular conditions, some of which have little in common with the disease for which the name was created. The term "necrotizing angiitis" is suggested by this investigator for the entire group of lesions. The other factor explaining the recent increased interest in this disease is the promising results obtained by ACTH and cortisone in the treatment of this previously "untreatable" disease. In one study the authors report on the treatment of eight patients with these drugs. It is quite astonishing to learn that these eight patients were only part of the total cases (14) admitted to one hospital during the years 1950-1955[1].

The pathology of *periarteritis nodosa* is best described as eccentric or segmental involvement of a small or medium-sized artery, characterized by inflammatory infiltration, intimal proliferation with occlusion of the lumen and hyaline necrosis of the media. The aneurysmal dilatations which often occur at the site of the lesions produce the appearance from which the name was derived. The lesion usually begins as a focus of degeneration in branchings and bifurcations. It is particularly prevalent where medium-sized arteries give rise to smaller

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vessels. Eventually the lesions are widely disseminated. They result in ischemia of the tissues supplied by the stenosed vessel and accordingly the clinical picture is characterized by inconsistency and multiplicity. Depending upon the localization of the pathological process, specific manifestations may develop in the skin, kidney, heart, nervous system, lungs or gastrointestinal tract. In this discussion we are primarily interested in calling attention to the very high incidence of abdominal signs and symptoms in this disease. Campbell[4] has noted that *periarteritis nodosa* involves the vessels of the gastrointestinal tract in from 50 to 100 per cent of the cases. The small caliber vessels of the hilar regions of abdominal viscera and near the mesenteric attachment to the intestine, are particularly prone to the pathological process in patients afflicted with this disease.

From the foregoing discussion of the pathological changes in *periarteritis nodosa* it is understandable that the changes in the gastrointestinal tract are protean. Acute catastrophic events such as intestinal perforation, gastric and intestinal ulceration with hemorrhage, acute appendicitis, acute cholecystitis and intraabdominal hemorrhage, may be the first indication of illness. Many cases of *periarteritis nodosa* are diagnosed by the surgeon at the operating table or by the pathologist upon examination of the surgical specimen. Campbell[4], reporting on five patients with signs of an acute abdomen due to *periarteritis nodosa*, has recently emphasized the responsibility of the surgeon in making the diagnosis. He states that *periarteritis nodosa* should be included in the differential diagnosis of abdominal disease, and at surgery if no other pathology is found, the arteries of the mesentery should be inspected for gross signs of the disease and a biopsy should be obtained if suspicious lesions are present. Polyarteritis involving the mesenteric arteries has often been reported, and a patient with acute ulcerative enteritis resulting from vascular thrombosis secondary to the inflammatory changes in the small arteries and arterioles has been described by Jernstrom and Stasney[5]. They conclude that polyarteritis is an occasional cause of intestinal ulceration and agree that the diagnosis of polyarteritis may sometimes be made by sigmoidoscopy in instances in which the large bowel is affected. A remarkable case was very recently reported by McKeown and Ganguli[6]. The outstanding feature of this case was that over an 11-month period the patient sustained and survived no less than six perforations of the jejunum. It is also interesting to note that this patient received therapy with ACTH and cortisone and the authors remark that cortisone therapy in patients with *periarteritis nodosa* has its limitations and perhaps contraindications. They comment that cortisone therapy may be a double-edged weapon. If the dose of cortisone is inadequate the disease progresses and intestinal ulceration persists with the hazard of further perforation. If, however, following an adequate dosage the arterial lesions heal, thrombosis may occur in the healing vessels and result in perforation of the ulcer because of ischemia. The clinician, faced with the problem, is reminded of the pros and cons of the use of steroid therapy in regional

enteritis and ulcerative colitis. Similar precautions are indicated when the gastrointestinal complications of *periarteritis nodosa*, featured by ulceration, occurs in the stomach.

Another group of abdominal signs and symptoms relating to the gastrointestinal tract have their site of origin in the liver and pancreas. Jaundice and enlargement of the liver are fairly frequent findings in patients with *periarteritis nodosa*. Jaundice, which was regarded by early investigators to be due to compression of the bile ducts by hepatic *periarteritis nodosa*, is now more commonly believed to arise from hemorrhagic infarctions elsewhere, as it has been often found that the liver may be free of lesions in the presence of considerable

TABLE I

SYMPTOMS AND SIGNS IN ORDER OF PREVALENCE IN 101 CASES OF PERIARTERITIS NODOSA

| Symptom or Sign | Number of Patients | Symptom or Sign | Number of Patients |
|---|---|---|---|
| Fever | 80 | Headache | 29 |
| Leucocytosis | 70 | Arthritis | 27 |
| Albuminuria | 65 | Atrophy | 25 |
| Hypertension | 64 | Visual disturbances | 23 |
| Rapid onset | 58 | Purpura | 22 |
| Abdominal pain | 57 | Cyanosis | 22 |
| Edema | 52 | Eosinophilia | 19 |
| Loss of weight | 48 | Nausea | 17 |
| Neuritis | 48 | Nodules | 16 |
| Hematuria | 47 | Pain in the chest | 16 |
| Dyspnea | 41 | History of allergy | 15 |
| Weakness | 41 | Convulsions | 15 |
| Emaciation | 36 | Icterus | 12 |
| Cough | 36 | Vertigo | 8 |
| Vomiting | 31 | Positive serological reaction | 8 |
| Sensory involvement | 31 | | |

jaundice. The opposite situation was found in the case reported by Plachta and Speer[7] where unusually severe damage of the liver due to periarteritis was found in a patient with no jaundice. Their case is interesting in regard to the unusual hypotension which was present in their patient. They suggest that VDM, the vasodepressor principle produced in the hypoxic liver may have been responsible for the continued hypotension in this case. Fatty liver is another common autopsy finding and attention has been called to the confusion in differential diagnosis between Wilson's disease and patients with periarteritis in association with hepatomegaly[8].

The pancreas is often found to be involved at autopsy in patients with *periarteritis nodosa* by the microscopic demonstration of an interstitial pancre-

atitis. Only a very few cases of the syndrome of acute pancreatitis have been described in the literature. There does not appear to be a higher incidence of diabetes mellitus in these patients. Splenic infarction and enlargement has also been reported.

Still another group of abdominal signs and symptoms are more difficult to evaluate and interpret. There are many patients with *periarteritis nodosa* who have vomiting, abdominal pain, melena, nausea, diarrhea, constipation and abdominal distention which are associated with relatively few structural altera-

TABLE II

First Symptom in Appearance in 220 Cases of Periarteritis Nodosa

| Symptom or Sign | Number of Patients | Symptom or Sign | Number of Patients |
|---|---|---|---|
| Malaise and weakness | 28 | Nausea and vomiting | 4 |
| Abdominal pains | 26 | Chill | 4 |
| Pains in legs | 26 | Paralysis of extremity | 3 |
| First symptom not reported | 25 | Diarrhea | 3 |
| Fever | 17 | Anorexia | 3 |
| Cough and dyspnea | 13 | Failing vision | 2 |
| Aches, pains (generalized) | 11 | Convulsive seizure | 2 |
| Parathesias | 10 | Nose bleed | 1 |
| Headaches | 9 | Coma | 1 |
| Skin lesions | 9 | Edema of face | 1 |
| Swelling and pain in joints | 8 | Pain in testicles | 1 |
| Pain in back | 8 | Gross hematuria | 1 |
| Pain in arms | 8 | Ataxia | 1 |
| Painful hands and feet | 8 | Facial paralysis | 1 |
| Edema of lower extremities | 7 | Paresis of eye muscles | 1 |
| Chest pain | 7 | Lymph node enlargement | 1 |
| Asthma | 6 | Polyneuritis | 1 |
| Sore throat | 5 | Purpura | 1 |
| Urticaria | 5 | Pain in neck | 1 |

tions of the alimentary canal. Some of these cases can be explained by early meningeal syndromes or terminal uremia, and others may be due to the by-products of extensive necrosis of organs distant from the gastrointestinal tract.

Symptoms referable to the gastrointestinal tract occur in over 50 per cent of the patients with *periarteritis nodosa*. Harris, Lynch, and O'Hare[9] have studied 101 cases of *periarteritis nodosa* and have compiled the symptoms and signs arranged in order of prevalence (Table I).

Table I gives an excellent over all review of the principal signs and symptoms of *periarteritis nodosa*. It is pertinent to note that 57 patients complained

of abdominal pain. Other symptoms and findings which are of particular interest from the gastroenterological aspect are the incidence of weight loss in 48 patients, weakness in 41, emaciation in 36, vomiting in 31, nausea in 17, and icterus in 12 patients.

In an attempt to facilitate the early diagnosis of *periarteritis nodosa* with special emphasis on the occurrence of gastrointestinal complications I have reviewed 220 cases in the American and English literature[10-113]. These cases were

TABLE III

| Age | Male | Females | Total |
|---|---|---|---|
| 0-4 | 1 | 5 | 6 |
| 5-9 | 3 | 4 | 7 |
| 10-14 | 6 | — | 6 |
| 15-19 | 6 | 6 | 12 |
| 20-24 | 14 | 4 | 18 |
| 25-29 | 14 | 2 | 16 |
| 30-34 | 13 | 9 | 22 |
| 35-39 | 22 | 5 | 27 |
| 40-44 | 20 | 4 | 24 |
| 45-49 | 9 | 5 | 14 |
| 50-54 | 9 | 5 | 14 |
| 55-59 | 7 | 7 | 14 |
| 60-64 | 8 | 7 | 15 |
| 65-69 | 4 | 3 | 7 |
| 70-74 | 1 | 1 | 2 |
| 75-79 | — | — | — |
| 80-84 | — | — | — |
| 85-89 | 12 | 1 | 13 |
| Unknown | 12 | 3 | 15 |
| Total | 149 | 71 | 220 |

taken at random from the literature, the only criteria being the availability of proven cases of *periarteritis nodosa*.

In the 220 cases reviewed in this survey an attempt was made to record the first symptom in appearance (Table II). There were many factors which made this difficult to determine. Many case reports were written in such a way that it was impossible to arrive at the first symptom of the disease. Many patients could not accurately determine the first symptom, and others stated that several symptoms began at the same time. The latter explains the listing of 269 "initial symptoms" for 220 patients. Although the above facts tend to minimize the importance of this study, it is felt that such an analysis perhaps can aid in the appreciation of the varied symptomatology of *periarteritis nodosa*.

Symptoms referable to the gastrointestinal tract were indicated as the presenting symptom in 36 patients, abdominal pain 26, nausea and vomiting 4, diarrhea 3 and anorexia 3.

In an attempt to gain more information other statistical studies were done. We were particularly interested in determining the sex and age prevalence as an aid in the diagnosis of *periarteritis nodosa*. The distribution as to age and sex in 220 cases of *periarteritis nodosa* reported at this time is shown in Table III.

This table again reveals the greater incidence of *periarteritis nodosa* in males and the peak incidence occurring between the ages of 20 and 40.

Incompleteness of many case reports and the tendency of the patient to merge complaints of the present illness with those of previous illnesses, make an accurate statement concerning past histories impossible. An attempt was made, however, to determine the incidence of previous gastrointestinal complaints as a contrast to the high incidence of abdominal complaints in those following the onset of the disease (Table IV).

It can be noted from the above list that the incidence of previous gastrointestinal disease is quite low. It is, however, of striking interest to observe the high incidence of diseases which are considered to be related to hypersensitivity. Bronchial asthma was found in 30 cases. "Other allergic diseases" (hay fever, hives, urticaria, etc.) was found to be present in seven histories. Outstanding is the fact that in 28 cases there was a history of the patient receiving sulfonamide therapy. There were 7 patients who had received rabbit or horse serum as therapeutic agents, and five patients with a history of hepatitis following yellow fever vaccination. These statistics tend to reveal a history of allergic reactions to drugs or foreign proteins which is in keeping with the more recent concepts of the etiology of *periarteritis nodosa*.

The early diagnosis of *periarteritis nodosa* remains an extremely difficult task despite the increasing awareness of the practicing physician. We have demonstrated again the wide variations that can exist in the clinical features of this disease. Ettinger and Pérez-Tamayo[114] reported the roentgen demonstration of ulcerative lesions of the small intestines in a patient with ulcerative jejunitis due to polyarteritis. As they clearly state, however, it is apparent that many of the macroscopic lesions seen at autopsy in polyarteritis do not lend themselves to roentgen recognition. Mucosal and submucosal hemorrhages, ischemia not leading to necrosis, scattered single ulcerations and minimal localized lesions cannot be detected by radiologic methods.

For many years great importance has been placed on muscle biopsy as the best method of facilitating the diagnosis of *periarteritis nodosa*. Maxeiner, McDonald, and Kirklin[115] have recently published an excellent study in an effort to evaluate muscle biopsy as a diagnostic procedure in this disease. Their results

revealed that positive findings were seen in 35 per cent of patients who actually had *periarteritis nodosa* and in 13 per cent of all the biopsies performed. Ninety-two per cent of the biopsies taken at random were valueless. The most favorable

TABLE IV

PREVIOUS ILLNESS RECORDED IN 220 PATIENTS WITH PERIARTERITIS NODOSA

| | |
|---|---|
| "Previously well" | 57 |
| Bronchial asthma | 30 |
| Sulfonamide drug received in therapy | 28 |
| No past history recorded | 28 |
| Syphilis | 12 |
| Gonorrhea | 11 |
| Pneumonia | 10 |
| Sore throat | 9 |
| Hypertension | 9 |
| Measles | 7 |
| History of other allergies | 7 |
| Serum received in treatment | 7 |
| Sinusitis | 6 |
| Yellow fever vaccine followed by hepatitis | 5 |
| Polyarthritis | 5 |
| Whooping cough | 3 |
| Mumps | 3 |
| Chicken pox | 3 |
| Malaria | 3 |
| Bronchitis | 3 |
| Scarlet fever | 2 |
| Nephritis | 2 |
| Pulmonary tuberculosis | 2 |
| Pleurisy | 2 |
| Enteritis | 2 |
| Gastric ulcer | 2 |
| Hyperthyroidism | 2 |
| Minor infections | 1 |
| Tuberculous meningitis | 1 |
| Erysipilas | 1 |
| Endocarditis | 1 |
| Influenza meningitis | 1 |
| Hypothyroid | 1 |
| Jaundice | 1 |
| Congenital heart disease | 1 |
| Cirrhosis | 1 |

conditions for obtaining positive results were the presence of a nodule at the site of biopsy in a case in which symptoms regardless of their severity were present for a period of six months or less. They concluded that muscle biopsy is a

poor diagnostic test for *periarteritis nodosa* and is of value only if positive results are obtained.

With the above factor in mind it was believed that a reevaluation of the significance of eosinophilia was in order. I shall not attempt to analyze the studies of the blood that were made in the 220 cases, besides the incidence of eosinophils in the peripheral blood. There is no doubt of the importance of a marked elevation in eosinophils, appearing in a patient with a multiplicity of symptoms, leading to a consideration of the diagnosis of *periarteritis nodosa*,

TABLE V

PERCENTAGE OF CASES WITH EOSINOPHILIA. (HIGHEST VALUE OF EOSINOPHILS REPORTED WAS TAKEN IN EACH CASE.)

| Eosinophilia | Number of Cases | Percentage of Cases |
|---|---|---|
| Not reported | 61 | 27.7 |
| 0-4% | 83 | 37.7 |
| 5-9% | 21 | 9.5 |
| 10-14% | 9 | 4.1 |
| 15-19% | 2 | .9 |
| 20-24% | 5 | 2.3 |
| 25-29% | 2 | .9 |
| 30-34% | 2 | .9 |
| 35-39% | 3 | 1.4 |
| 40-44% | 3 | 1.4 |
| 45-49% | 4 | 1.8 |
| 50-54% | 2 | .9 |
| 55-59% | 3 | 1.4 |
| 60-64% | 0 | 0 |
| 65-69% | 3 | 1.4 |
| 70-75% | 11 | 5.0 |
| | 6* | 2.7* |
| Total number of cases | 220 | |

*Eosinophilia mentioned in case reports as "significantly elevated," but actual percentage of eosinophils not reported.

the percentage of these cells may be very high, in the range of 70-80 per cent of the white blood cells. Various studies have revealed, however, that in only about 12 per cent of the cases is there a significant eosinophilia. Some workers feel that this low incidence of eosinophilia is misleading and that if an opportunity is had to follow a case long enough an elevation of the eosinophila count will be observed at some stage.

In the present series of cases the highest elevation of the eosinophils was noted in each case report. Unfortunately in 27.7 per cent (61 cases) there was

no report of differential blood counts so that a determination of the true incidence of eosinophilia is not accurate. As will be observed in Table V, 37.7 per cent (83 cases) had from 0-4 per cent eosinophils, which is considered in the range of normalcy, whereas 34.6 per cent (76 cases) had a significant eosinophilia.

The finding of eosinophilia of significance in 34.6 per cent (76 cases) is to be emphasized. Several explanations can be given for the higher incidence in the past 20 years. There are more complete case reports with more frequent differential white counts; early diagnosis affording a longer period of follow-up of the patient; and probably of most significance, the increase in the use of therapeutic agents which are prone to cause hypersensitization with a resultant eosinophilia characteristic of these states, as Wilson and Alexander[117] have shown in their studies of bronchial asthma.

## Comment

The varied clinical manifestations of *periarteritis nodosa* and the absence of a laboratory test other than positive biopsy or eosinophilia, which is only of value in a relatively small number of cases, continue to cause great difficulties in the early diagnosis of *periarteritis nodosa*. While certain combinations of symptoms and signs are so characteristic as to be diagnostic, no experienced physician is unfamiliar with the case in which a seemingly probable diagnosis of *polyarteritis nodosa* has been disproved at necropsy[118].

Boyd[8] has stated that when the clinical picture of low grade sepsis is present and vague abdominal pain, usually located in the epigastrium or shifting from left to right, occurs in the course of a subacute or prolonged febrile illness, *periarteritis nodosa* should be considered if polyneuritis appears; if nephritis occurs or there is evidence of unexpected peritonitis it is additional reason to suspect *periarteritis nodosa*. To this we would add certain other diagnostic clues which are apparent from the foregoing statistical studies. A multiple system syndrome appearing between the second and fourth decade is to be highly suspected. A history of previous allergic disease and the presence of a significant eosinophilia are strong indications for the diagnosis of *periarteritis nodosa* in such patients.

The diagnosis often can only be made by exploratory laparotomy which in some cases may be life-saving. Subsequent medical treatment with cortisone and ACTH may be of equal value.

## Summary

Although there is an increased awareness of *periarteritis nodosa* and many more cases are now being reported, the disease remains difficult to diagnose. The variable clinical picture has been discussed with special emphasis on the gastroenterological aspects of the disease. A review of 222 proven cases of *peri-*

*arteritis nodosa selected* from the American and English literature is presented with statistical studies relating to symptoms, age and sex and the significance of eosinophilia. With the use of early laparotomy and the early institution of cortisone therapy the prognosis of *periarteritis nodosa* has improved. There are, however, certain complications of the gastrointestinal tract in *periarteritis nodosa* where cortisone and ACTH must be used with caution. Ulcerated intestinal syndromes such as colitis and jejunitis may be contraindications to the use of steroid therapy.

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## Discussion

*Dr. Linn J. Boyd (New York, N. Y.):*—I noticed Dr. Nightingale had a little difficulty in a sense of referring at times to *periarteritis nodosa* and, at others, to polyarteritis. As a matter of fact, there are 26 synonyms in the literature, and the reason for that is that this is not a disease. It is a vascular reaction and this reaction may occur in any particular patient and in any artery. As Dr. Nightingale pointed out it is primarily a lesion of the muscular arteries which are a little smaller than the hepatic arteries.

My own interest in this disease—and I won't take up too much time—began 20 years ago when one of my surgical colleagues presented the syndrome of an acute gallbladder. A cholecystectomy was performed but the symptomatology continued. About three months later he died, and at necropsy showed a typical universal *periarteritis nodosa*. Review of the original tissue revealed a classical *periarteritis nodosa;* in other words, one of the diagnostic features that should be emphasized is that in an abdominal catastrophe for which surgery is performed, and unless the pathologist pays particular attention to this possibility, it is very easy to overlook the lesion. Consequently, I would urge a special search for periarteritic lesions in any of the acute abdominal viscera at the time tissue is removed.

There is only one other point I should like to make which strikes me as being of great interest. *Periarteritis nodosa* is the only febrile disease with which I am acquainted in which suddenly in the course of the illness, in a fair percentage of cases, a decided hypertension develops. I think to me that is more important than the eosinophilia.

# ENZYME ACTIVITY IN THE SERUM AND COMMON DUCT BILE OF DOGS

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The elevation of the serum enzymes glutamic oxalacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) in patients with obstructive jaundice[1,2] suggested that the biliary system might serve as an excretory pathway for enzyme activity. The observation that gallbladder bile contained high enzyme activity[3] and that ligation of the common bile duct in rats was followed by an immediate increase in serum GOT activity which subsided promptly after release of ligation[4] also fitted with this hypothesis. It is now apparent, however, that biliary obstruction in humans is not invariably accompanied by rises in serum GOT[5,6] and further work by Chinsky et al with common duct-ligated rats demonstrated immediate serum GOT and GPT rises followed by declining levels in spite of continuing obstruction[7]. In an effort to correlate serum and biliary enzyme levels Pellegrini measured GOT in rabbit gallbladder bile, but found great variability even in identical samples from one individual[8].

The present study was initiated to determine whether a significant portion of serum enzyme activity is excreted via the biliary system.

## Methods

*Animals and surgery:*—1. Female mongrel dogs were subjected to cholecystectomy and division of the common bile duct with cannulation of its proximal end.

2. The internal glass cannula led to an external condom-reservoir via gum rubber tubing. Bile was removed from the reservoir under antiseptic conditions at least daily.

3. Dogs were fed on lean horse meat to which Tween 80, one teaspoon per feeding, was added. Vitamins A, D, C, B-complex, and K were used as dietary supplements. Antibiotics (terramycin or chloromycetin) were given daily P. O. Animals remained in good health for months on this schedule.

*Enzyme determinations:*—1. GOT and GPT were measured by the methods of Karmen et al[9] and Wroblewski and LaDue[2], respectively.

2. Lactic dehydrogenase (LDH) was measured by the method of Wroblewski and LaDue[10].

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3. Common duct bile was dialyzed for 24 hours in the cold against .005 M phosphate buffer, pH 7.4, prior to enzyme analysis. Meister et al reported that such dialysis produces no loss in GOT activity[11]; this was also confirmed for GPT and LDH in this laboratory. Dialysis was required to reduce the intensity of the bile sample blank on the Beckman DU spectrophotometer.

4. Samples of dialyzed common duct bile at room, refrigerator and freezer temperatures were measured daily over a 2-week period. GOT, GPT, and LDH showed no loss of activity during the first week when stored in refrigerator or freezer. All samples collected were stored in the refrigerator and analyzed within a week of collection.

TABLE I

Enzyme Levels Following Exposure to $CCl_4$ Vapor

| Enzyme | Hours postexposure | | | | |
|---|---|---|---|---|---|
| | 0 | 24 | 36 | 60 | 132 |
| *Serum* | | | | | |
| GOT | 15 | 76 | 279 | 194 | 116 |
| GPT | 33 | 58 | 259 | 397 | 233 |
| LDH | 192 | 100 | 138 | 248 | 153 |
| *Bile* | | | | | |
| GOT | 20 | 19 | 13 | | 7 |
| GPT | 3 | 4 | 5 | 5 | 3 |
| LDH | 12 | 27 | 26 | 26 | |

5. Preparation of GOT concentrates was done by the method of O'Kane and Gunsalus[12]. 25 $\mu$ g. of pyridoxal phosphate* were added to the test mixture prior to each analysis in experiments involving the GOT concentrate. The LDH used for intravenous administration was obtained commercially†.

## Results

*Enzyme activity in the bile of control animals:*—Daily enzyme measurements, for periods of 2 to 7 weeks, were performed on the bile of 5 animals under simple maintenance conditions. GOT activity ranged from 0 to 64, GPT from 0 to 23, and LDH was 0 to 105 units/ml./min. Each animal produced approximately 60 to 100 c.c. of bile per day. When total daily enzyme output was calculated (units/ml./min. x ml. bile), the variability remained unchanged.

*California Foundation for Biochemical Research, Los Angeles, Calif.
†Worthington Biochemical Corp., Freehold, N. J.

*Carbon tetrachloride administration:*—One dog was exposed to $CCl_4$ vapor (approximately 200 ppm. for 5 hours) and serial measurements of enzyme activity in bile and serum were made for 130 hours postexposure. The results are shown in Table I.

TABLE II

ENZYME LEVELS FOLLOWING INJECTION OF GOT CONCENTRATE

| Time postinjection | GOT serum | GOT bile | GPT serum |
|---|---|---|---|
| 0 | 28 | 16 | 23 |
| 10 min. | 518 | | |
| 6 hours | 303 | 15 | 31 |
| 24 hours | 36 | 13 | 24 |
| 48 hours | | 23 | |

The bile output of the animal represented above remained constant at approximately 90 c.c. per day. A second dog, however, which received 5 c.c. of $CCl_4$ via gastric tube had an immediate, complete shutdown of bile production. Patency of the fistula was demonstrated by roentgenographic studies. This animal has had only a 5-lb. weight loss and very gradually developing icterus

TABLE III

ENZYME LEVELS FOLLOWING INJECTION OF LDH CONCENTRATE

| Time postinjection | LDH serum | LDH bile |
|---|---|---|
| 0 | 155 | 14 |
| 10 min. | 2280 | |
| 5 hours | 108 | 13 |
| 24 hours | 91 | 29 |
| 48 hours | | 67 |

for the past 3 months in spite of total absence of bile production. Serum enzyme levels are presently: GOT 157, GPT 335, and LDH 250.

*Enzyme injection:*—Two dogs were given intravenous injections of GOT concentrate (10 c.c., 150,000 units/ml./min.). Serum and bile were then serially analyzed for enzyme activity. Results in both animals were similar. Table II presents data from one experiment.

Very rapid fall-off in serum LDH activity following intravenous administration of LDH has been reported by Wroblewski and LaDue[10]. Accordingly, on two occasions a dog was given intravenous LDH concentrate (1 c.c., 800,000 units/ml./min. diluted to 30 c.c. with normal saline). Serum and bile were serially analyzed for enzyme activity. Both experiments gave similar results. Typical data are recorded in Table III.

It would be expected that the rapid disappearance of serum LDH would be reflected in increased bile LDH activity if this route represented a significant excretory pathway of active enzyme. The same reasoning would apply to GOT, although we did not achieve the high serum levels reported by Fleischer and Wakim[13] with the use of GOT concentrates. Therefore, while it is possible to obtain consistent and reproducible enzyme determination on bile, the hope that such determinations would be useful in the differential diagnosis of jaundice[5] does not appear to be justified.

## Summary

1. Total biliary fistulas were surgically created in 5 dogs, and analyses of glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) and lactic dehydrogenase (LDH) activities were accomplished on the collected common duct bile.

2. Under basal conditions common duct bile contained between 0-64 units/ml./min. of GOT, 0-23 units/ml./min. of GPT, and 0-24 units/ml./min. of LDH activity.

3. After exposure of one dog to $CCl_4$ vapor, serum GOT and GPT activity rose to over 10 times control values. No corresponding increase was found in the bile.

4. After intravenous administration of GOT and LDH concentrates, serum levels of these enzymes rose to approximately 15 times control levels. Again, no corresponding increase was found in the bile.

## Acknowledgement

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# CLINICAL EVALUATION OF PAPER ELECTROPHORESIS

## VI. Normal Serum Lipid Partitions and Normal Serum Protein Fractions as a Function of Age and Sex

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A sufficiently large series of carefully selected serum specimens from normal subjects of ages 12 to 100 years were studied by filter paper electrophoresis by one of the authors (AAG). The object was to establish the relative distribution of lipoproteins in the serum of these individuals as a function of age and sex. The statistical analysis revealed that there is no relationship between age and sex upon the serum lipoprotein distribution. One may have a single average for all individuals regardless of sex[1].

There is no complete agreement as to the findings of some that there are no significant sex, age, or racial differences in the concentration of serum lipid partitions and serum proteins. Simultaneous sera in these normal hospitalized patients and personnel mentioned above were examined for the varied serum lipid and serum protein fractions as a function of age and sex[1].

### Material Studied

Hospitalized male and female normal patients ranging in ages from 12 to 100 years were studied. They were postoperative subjects from the varied surgical services and individuals from the medical services. In addition, the bloods of medical students, house physicians, nurses, and hospital personnel were examined.

There were no metabolic, hepatic, cardiovascular, nor coronary artery diseases, nor any condition which would have any questionable effect upon the final determinations. Age, sex, color, weight, clinical and nutritional status were noted, so that "normal" conditions would prevail.

### Methods of Study

Fasting nonoxalated blood, 15 c.c., was obtained and the serum was utilized. Duplicate samples of the serum were analyzed. The lipid phosphorus (lipid

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esters of phosphoric acid) were determined by the Youngburg modified digestive method[2]; Phospholipid values were obtained by multiplying the lipid phosphorus determinations by the factor 25. Total lipids were determined by the gravimetric modified Bloor method[3]. Total cholesterol and esters were determined by the Leiboff method[4]. In order to express the value of cholesterol esters in terms of actual weight, a factor of 1.67 was utilized. This figure was obtained by dividing the molecular weight of cholesterol oleate by the molecular weight of cholesterol. Neutral fats were obtained indirectly by subtracting from the total lipid values the weights of the phospholipids, free cholesterol, and cholesterol oleate fractions. Lipid fraction percentages were calculated by dividing the weights of the various lipid fractions by the total lipids. The total protein, albumin and globulin values were obtained by the Tyrosine method of Greenberg[5].

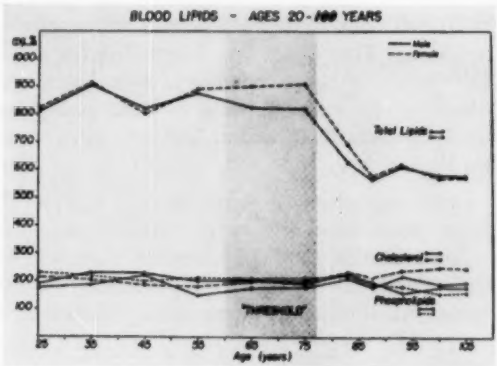


Fig. 1—Serum lipid partitions in "Normal" individuals, aged 25 to 100 years, showing no significant variations and "Threshold" age group of 60 to 75 years. From *A.M.A. Arch. Int. Med.* **97**:359-381 (March), 1956[15].

The detailed explanations of the methods were discussed in previous publications for the serum lipid partitions[6,7] and the filter paper electrophoresis[1,8,9].

## Results

The serum partitions examined were those of the varied serum lipid fractions and its percentage values of the total serum lipids. The chemical determination of total serum proteins, albumin and globulin was performed. These results were compared to the serum protein and lipoprotein values obtained by filter paper electrophoresis, as mentioned in other publications[1,8,9]. The object was to show the weakness and inaccuracy of the present chemical determinations of serum proteins in diseases, especially of liver disturbances. Filter paper electrophoresis reveals a more exact picture of the underlying chemical and physiological disturbances.

First, the patients were sorted into sexes. There were 49 males and 34 females, total of 83 for both sexes, for the serum lipid and total protein determinations. The serum lipoprotein groups contained a total of 103 patients, with 58 males and 45 females.

Patients with hepatic disease constituted a group of 28 males. The normal individuals in the 80-100 year group were a total of 75, with 36 males and 39 females. All of the above determinations were utilized for comparative purposes.

## Statistical Analysis of Data

The mean levels of various serum partitions were computed for each 10-year age group and sex for 49 normal males and 34 normal females, between the ages of 11 and 80 (Table I). The standard deviations were computed for each

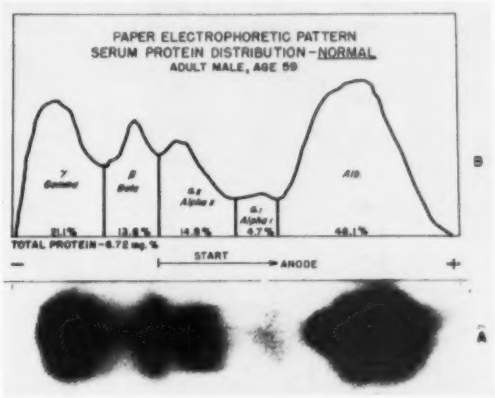


Fig. 2—Comparison of dyed filter paper electrophoretic pattern (A) and corresponding densitometered and planimetered pattern (B) of serum proteins in *a normal adult male*, age 59. The A/G ratio from the percentage components is 0.85. The total protein 6.72 mg. per cent and A/G ratio 1.7:1 (Clinical determination). The five normal bands of the serum proteins are present.

sex since there was no evidence that the variability within each group was different from one age group to another.

The formula used for the standard deviation was:

$$\delta\,(s,\ \text{sigma}) = \sqrt{\frac{\Sigma\,(X^2)}{N\text{-}1}}$$

$\delta$ (sigma) = Standard deviation.
X = Deviations from arithmetic mean.
N = Total number of observations.
$\Sigma\,(X^2)$ = Sum of deviations squared.

TABL

MEAN LEVELS AND STANDARD DEVIATIONS OF SERU
CENTAGES IN TERMS OF TOTAL SERUM LIPID VALUE

| Age | No. Cases | Total Protein | Total Lipids | Cholesterol | | | Esters |
|---|---|---|---|---|---|---|---|
| | | | | Total | Free | | |
| | | | | | | %° | |
| Males | | | | | | | |
| 11-20 | 3 | 7.15 | 846 | 203 | 78 | 9.2 | 126 |
| 21-30 | 14 | 7.20 | 757 | 220 | 82 | 10.8 | 138 |
| 31-40 | 9 | 6.87 | 793 | 212 | 82 | 10.0 | 131 |
| 41-50 | 7 | 6.68 | 788 | 214 | 82 | 10.4 | 133 |
| 51-60 | 6 | 6.91 | 835 | 248 | 104 | 12.5 | 144 |
| 61-70 | 6 | 7.65 | 865 | 238 | 91 | 10.5 | 147 |
| 71-80 | 4 | 6.71 | 798 | 203 | 75 | 9.4 | 127 |
| Mean | 49 | 7.04 | 799 | 221 | 85 | 10.6 | 136 |
| Std. Dev. | | 0.54 | 58 | 27 | 19 | ± 1.6 | 22 |
| Females | | | | | | | |
| 11-20 | 4 | 6.87 | 818 | 222 | 78 | 9.8 | 143 |
| 21-30 | 8 | 6.90 | 781 | 229 | 91 | 11.1 | 124 |
| 31-40 | 5 | 6.90 | 761 | 199 | 69 | 9.0 | 129 |
| 41-50 | 4 | 7.22 | 847 | 201 | 75 | 8.8 | 125 |
| 51-60 | 7 | 6.96 | 736 | 212 | 83 | 11.3 | 129 |
| 61-70 | 3 | 6.65 | 782 | 200 | 89 | 11.4 | 111 |
| 71-80 | 3 | 7.33 | 905 | 255 | 94 | 10.4 | 161 |
| Mean | 34 | 6.96 | 792 | 216 | 83 | 10.4 | 130 |
| Std. Dev. | | 0.47 | 77 | 29 | 10 | ± 1.5 | 23 |
| Both Sexes | | | | | | | |
| 11-20 | 7 | 6.99 | 830 | 214 | 78 | 9.6 | 136 |
| 21-30 | 22 | 7.09 | 766 | 224 | 86 | 11.0 | 134 |
| 31-40 | 14 | 6.88 | 782 | 207 | 77 | 9.6 | 130 |
| 41-50 | 11 | 6.98 | 809 | 209 | 79 | 9.8 | 130 |
| 51-60 | 13 | 6.93 | 780 | 228 | 92 | 11.8 | 135 |
| 61-70 | 9 | 7.31 | 837 | 226 | 90 | 10.7 | 135 |
| 71-80 | 7 | 6.99 | 844 | 225 | 83 | 9.8 | 142 |
| Mean | 83 | 7.01 | 796 | 219 | 84 | 10.5 | 133 |
| Std. Dev. | | 0.51 | 66 | 27 | 16 | ± 1.5 | 22 |

+ = Factor 1.67 x cholesterol ester values = esterified cholesterol[6,7].
° Lipid fraction percentages were calculated by dividing the weights of the various li
°° Ratio phospholipids to total cholesterol (P/C Ratio—Units).

I

LIPID PARTITIONS (MG. PER 100 ML. SERUM) AND PER-
NORMAL SUBJECTS, AGE 11-80, BY SEX AND AGE GROUP

| Esterified Cholesterol | | Lipid-phosphorus | Phospho-lipids | | Neutral Fats | | P/C Ratio |
|---|---|---|---|---|---|---|---|
| Mg.* | %° | | | %° | | %° | Units°° |
| 209 | 24.7 | 8.7 | 218 | 25.7 | 342 | 40.4 | 1.07 |
| 231 | 30.5 | 8.1 | 204 | 26.9 | 241 | 31.8 | 0.92 |
| 218 | 26.5 | 8.2 | 204 | 24.8 | 319 | 38.7 | 0.96 |
| 222 | 28.2 | 8.3 | 207 | 26.3 | 276 | 35.1 | 0.96 |
| 241 | 28.9 | 8.5 | 211 | 25.3 | 279 | 33.3 | 0.85 |
| 245 | 28.3 | 8.7 | 218 | 25.2 | 312 | 36.0 | 0.91 |
| 212 | 26.6 | 8.3 | 207 | 25.9 | 304 | 38.1 | 1.02 |
| 227 | 28.2 | 8.3 | 208 | 25.8 | 285 | 35.4 | 0.94 |
| 37 | ± 5.6 | 0.5 | 13 | 2.3 | 87 | 9.2 | 0.14 |
| 240 | 30.3 | 8.7 | 217 | 27.4 | 258 | 32.5 | 0.98 |
| 233 | 28.4 | 8.1 | 204 | 24.9 | 291 | 35.6 | 0.89 |
| 216 | 28.3 | 8.0 | 200 | 26.3 | 277 | 36.4 | 1.01 |
| 209 | 24.6 | 8.6 | 216 | 25.6 | 348 | 41.0 | 1.07 |
| 216 | 29.3 | 8.5 | 213 | 28.9 | 224 | 30.5 | 1.00 |
| 185 | 23.7 | 8.4 | 210 | 26.9 | 298 | 38.0 | 1.05 |
| 269 | 29.7 | 8.5 | 213 | 23.5 | 329 | 36.4 | 0.84 |
| 224 | 28.1 | 8.4 | 209 | 26.2 | 282 | 35.3 | 0.97 |
| 38 | 5.2 | 0.5 | 14 | 3.5 | 58 | 8.1 | 0.12 |
| 227 | 27.8 | 8.7 | 217 | 26.6 | 294 | 36.0 | 1.01 |
| 232 | 29.7 | 8.1 | 204 | 26.1 | 259 | 33.2 | 0.91 |
| 217 | 27.1 | 8.1 | 202 | 25.2 | 304 | 38.1 | 0.98 |
| 217 | 26.8 | 8.4 | 211 | 26.1 | 302 | 37.3 | 1.01 |
| 228 | 29.2 | 8.5 | 212 | 27.1 | 250 | 31.9 | 0.93 |
| 225 | 26.9 | 8.6 | 215 | 25.7 | 307 | 36.7 | 0.95 |
| 237 | 28.0 | 8.4 | 210 | 24.9 | 315 | 37.3 | 0.93 |
| 226 | 28.1 | 8.3 | 208 | 26.0 | 283 | 35.4 | 0.95 |
| 37 | ± 4.6 | 0.5 | 13 | ± 2.9 | 70 | ± 7.6 | 0.13 |

actions by the total lipids[6,7].

The "F-test" was then made to see if there were any differences in the mean levels of the partitions by age groups[10]. With one exception (Total Lipids-Females) there were no differences due to age group within sex. In the one significant difference, the high values for total lipids for 3 females, 71-80, accounted for most of the variation.

Subsequent tests revealed the standard deviations and means for both sexes were not significantly different and the combined values were formed for all 83 individuals (Table I).

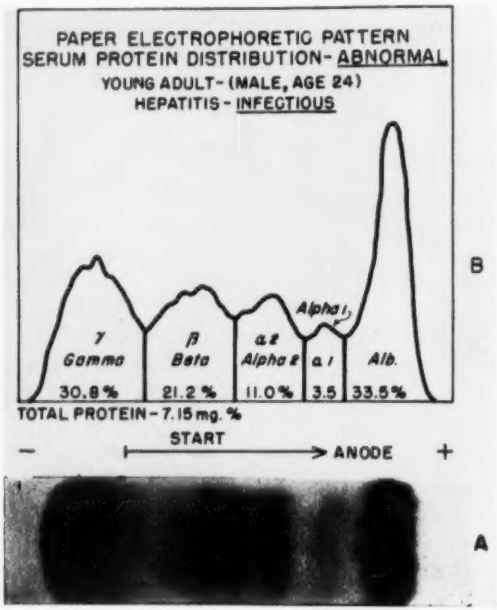


Fig. 3—Dyed filter paper electrophoretic strip (A) and corresponding pattern (B) of serum proteins. Young male, age 24. Diagnosis:—*Infectious hepatitis*, in a narcotic addict. Pattern shows slightly diminished albumin and moderately increased gamma components. A/G ratio 0.50. Total protein 7.15; albumin 3.79; globulin 3.36 mg. per cent, A/G ratio 1.10 (Chemical determination). Electrophoretic results of greater value than chemical determination, clinically, are shown.

These results were compared with values for normal middle aged subjects (Table II-A) performed at an earlier date by one of us (AAG). The means for phospholipids, total cholesterol, cholesterol esters, and free esters were within limits of expected variation. Neutral fats, total lipids and P/C ratio values shown in Table II-A were considerably higher than for those computed here. This discrepancy cannot be explained on the basis of the available data. The technic, then, was slightly different than the present.

TABLE II

ARITHMETICAL MEAN AND STANDARD DEVIATION VALUES OF SERUM LIPID PARTITIONS (MG. PER 100 ML. SERUM) AND PERCENTAGES IN TERMS OF TOTAL SERUM LIPID VALUES IN NORMAL (AGE 11-100), AND HEPATIC DISEASED (AGE 23-84) INDIVIDUALS

| Status of Patients | Total Lipids | Lipid-phosphorus | Phospho-lipids | Cholesterol | | | | | | Neutral Fats | Ratio of Phospholipids to Total Cholesterol | Lipid Fraction % | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total | Ester | % of Total | Esterified | Free | % of Total | | | Free | Esterified | Phospho-lipids | Neutral Fats |
| A. Normals (Middle Adult, Age 46) | | | | | | | | | | | | | | | |
| Mean | 861 | 8.6 | 218 | 197 | 121 | 61.2 | 202 | 76 | 38.8 | 365 | 1.10 | 9.1 | 23.5 | 25.3 | 42.1 |
| B. Normals (Age 11-80) | | | | | | | | | | | | | | | |
| Mean | 796 | 8.3 | 208 | 219 | 133 | 61.0 | 226 | 84 | 38.3 | 283 | 0.95 | 10.5 | 28.1 | 26.0 | 35.4 |
| Std. Dev. | 66 | 0.5 | 13 | 27 | 22 | — | 37 | 15 | — | 70 | 0.13 | 1.5 | 4.6 | 2.9 | 7.6 |
| C. Normals (Age 80-100) | | | | | | | | | | | | | | | |
| *Males* | | | | | | | | | | | | | | | |
| Mean | 611 | 7.76 | 194 | 203 | 126 | 62.0 | 210 | 77 | 38.0 | 196 | 0.95 | 11.3 | 31.1 | 28.7 | 28.9 |
| Std. Dev. | 77.9 | — | 31.0 | 41.1 | 26.9 | — | | 16.5 | — | 98.7 | 0.14 | — | — | — | — |
| *Females* | | | | | | | | | | | | | | | |
| Mean | 645 | 7.68 | 192 | 230 | 161 | 70.0 | 269 | 69 | 30.0 | 264 | 0.83 | 8.7 | 33.9 | 24.2 | 33.2 |
| Std. Dev. | 187.5 | — | 32.7 | 31.3 | 28.5 | — | | 20.8 | — | 88.0 | 0.14 | — | — | — | — |
| D. Hepatic Disease (Age 23-84) | | | | | | | | | | | | | | | |
| Mean | 756 | 7.1 | 180 | 283 | 162 | 57.2 | 271 | 121 | 42.8 | 197 | 0.63 | 15.7 | 35.2 | 23.4 | 25.7 |
| Std. Dev. | 173 | 0.8 | 23 | 61 | 47 | — | 90 | 57 | — | 87 | 0.38 | 4.41 | 8.60 | 4.46 | 11.0 |

Comparisons between data for 80-100 year old normal subjects in Table II-C and results obtained in the present investigation (Tables I, II-B) showed standard deviations were generally higher for the older group than for normal subjects under 80 years of age. Mean values for neutral fats and total lipids for the 80-100 group were significantly lower than those for the group in this study, but no other differences were detected here.

In the hepatic diseased subjects, one notes that the total serum lipids and phospholipids are moderately diminished, but the neutral fats, markedly diminished. The lipid fraction percentages reveal a similar reduction in the phospholipid and neutral fat fractions, with an increase of the free and esterified cholesterol partitions (Table II-D).

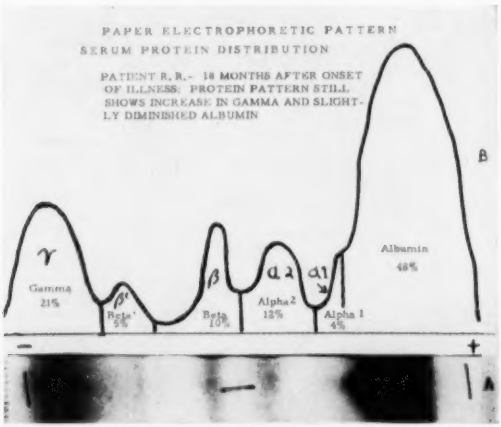


Fig. 4—Dyed filter paper electrophoretic strip (A) and corresponding pattern (B) of serum proteins. Young male, age 23. Diagnosis:— *Virus hepatitis severe with jaundice*—18 months after onset. Pattern of protein distribution still shows *increased gamma* and slightly *diminished albumin* components. A/G ratio 0.92. Total proteins 6.40; albumin 4.19; globulin 2.21 mg. per cent; A/G ratio 1.90 (Chemical determinations). Paper electrophoretic pattern still abnormal in the presence of normal chemical fractionations.

More information is available to the physician from the serum protein fractionation by the paper electrophoretic than by the chemical method (Table III). While the total proteins and A/G ratio are less in the hepatic disease patients than in the normals, yet comparatively it does not reveal the actual abnormal changes in the low serum albumin and increased serum gamma globulin components of the electrophoresis (Table III). This holds true for the A/G ratio of 1.18 (chemical) compared to A/G ratio of 0.42 (electrophoretic). It, therefore, will be misleading in many diseases for the clinician to be guided by the chemical serum protein fractionation alone.

TABLE III

COMPARISON OF SERUM PROTEIN FRACTIONATION VALUES BY FILTER PAPER ELECTROPHORETIC AND CHEMICAL METHODS IN NORMAL AND HEPATIC-DISEASED INDIVIDUALS. NORMAL SERUM LIPOPROTEIN VALUES BY PAPER ELECTROPHORESIS METHOD

| Serum Components | Filter Paper Electrophoresis—Relative Concentration in Percentages | | | | | | Chemical Method—gm. per 100 ml. | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Normals | | | | Hepatic Disease | | Normals | | | | Hepatic Disease | |
| | Protein Values | | Lipoprotein Values (Age 11-100) | | Protein Values (Age 23-84) | | Age 12-80 | | Age 80-100 | | Age 23-84 | |
| | Mean | Standard Deviation | Mean | Standard Deviation | Mean | Standard Deviation | Mean | Standard Deviation | Mean | Standard Deviation | Mean | Standard Deviation |
| Total Protein | — | — | — | — | — | — | 7.01 | ±0.51 | 6.59 | ±0.97 | 6.68 | ±0.64 |
| Albumin | 42.5 | ±3.9 | — | — | 29.2 | ±6.8 | 4.23 | ±0.48 | 3.94 | ±0.79 | 3.53 | ±0.55 |
| Globulin | — | — | — | — | — | — | 2.78 | ±0.34 | 2.65 | ±0.46 | 3.10 | ±0.59 |
| Alpha-1 | 5.1 | ±1.8 | 23.3 | ±7.1 | 6.3 | ±1.8 | | | | | | |
| Alpha-2 | 11.3 | ±3.3 | 9.1 | ±3.6 | 11.6 | ±3.8 | | | | | | |
| Beta | 19.0 | ±2.7 | 42.4 | ±7.8 | 18.6 | ±4.8 | | | | | | |
| Gamma | 22.1 | ±2.6 | 25.4 | ±7.5 | 33.9 | ±8.8 | | | | | | |
| A/G Ratio | 0.72 | ±0.29 | — | | 0.42 | ±0.14 | 1.52 | ±0.25 | 1.50 | ±0.33 | 1.18 | ±0.29 |
| "Beta" Group / "Alpha" Group Ratio | | | 2.11:1 | | | | | | | | | |

*Alpha-1 + alpha-2 lipoproteins = "Alpha" group. Beta + gamma lipoproteins = "Beta" group[1].

## Comment

The significance of much of the reported data on sex and age differences in plasma cholesterol and lipids is difficult to evaluate[11]. This may be due to the differences in analytical technics, technical variability, and nonspecificity of the difficult analytical methods. Despite the abundance of cholesterol in human blood and the many discussions about its significance, descriptions of "normal" levels have been diffuse and often inconsistent[12]. Although there is no complete agreement that there is no significant sex or racial difference in the concentrations of plasma lipids, there is evidence that "adult" patterns of blood lipid concentrations are established at an early age, and change but little, if at all, in later years in normal subjects[11].

In a study of "normal" individuals age 80-100 years, it was shown that the cholesterol values, except for an insignificant rise in the older female group, showed no significant variations in any age group[13,14]. Phospholipid values showed no variation (Table II-C). Total serum lipids decreased significantly after the age group of 60 to 75 years. This was termed the "Threshold Age", during which there may be a decline or reversal of biochemical and/or physical processes. There was no difference between the male and female groups[15,16] (Fig. 1).

Human plasma contains 90-92 per cent water. Blood owes much of its physiological importances to its high water content. Proteins form most of the solid matter of plasma. They total between 6-7 per cent of the plasma. They include fibrinogen, serum albumin and serum globulin.

With the advent of new technics for the analysis of the constituents of plasma, a large body of knowledge concerning the plasma proteins is becoming available. At the present time, the electrophoretic method of analysis of plasma or serum proteins has its greatest values in studying the relative amounts of various components present (Table III) and the changes which these components undergo during diseases with a view to possible aid in diagnosis and prognosis[8,9] (Figs. 2, 3 and 4).

The literature contains much conflicting data, not only concerning abnormal patterns but the "normal" as well, which may vary from author to author. Some observers stated that the effect of aging on serum protein is not apparent in human beings[17]. Others maintain that available information with respect to age changes in various blood constituents has been singularly lacking[18].

The statistical analysis of the 83 normal subjects, age 11-80, reported herein, revealed the mean levels and standard deviations for both sexes were not significantly different (Table I). By the "F-test", it was shown that there was no difference due to age group within sex. Standard deviations were generally higher for the older group of 80-100 years (Table II-C) than for the normal subjects under 80 years of age (Tables II-A, II-B). This would infer that there

is greater variability in the older than the younger people. *These observations definitely show that age and sex have no effect upon values obtained in normals.*

The quantitative measurement of serum total proteins with its separation into albumin and globulin components, has become a routine laboratory determination. This test is done for evaluating patients with malnutrition, dehydration, and liver disease, since the liver is the main source of serum proteins. Total protein concentration may offer less information, as well as the A/G ratio in diseases of liver disturbance. The fractionation by electrophoresis is of greater value for diagnosis and revealing the underlying disturbed physiology and pathology as shown in the patients herein discussed (Tables II-D, III).

The simplicity, inexpensiveness, and micro-range of sampling should make this procedure more available to the physician as a clinical laboratory method (Figs. 2, 3 and 4).

## Summary and Conclusions

1. Normal male and female patients, aged 12-100 years were studied for the varied serum lipid and serum protein fractions as a function of age and sex.

2. The mean levels and standard deviations for either sex and the varied age groups revealed no significant difference.

3. There was no evidence that the variability within each group was different from one age group to another as shown by the "F-test".

4. After age 80, there is a drop of the total serum lipids and neutral fats.

5. "Normal" values for varied serum lipid partitions and total serum proteins with its components were obtained for either sex in ages from 12 to 100.

6. It was *definitely shown that age and sex have no effect upon values obtained in normals.*

7. Fractionation of serum proteins by electrophoresis is more accurate; of greater aid in diagnosis; and gives a better understanding of the underlying physiology and pathology.

8. Chemical determination of total serum proteins and A/G ratio may offer less information and be of less clinical help to the physician, in many diseased states, than the electrophoretic results.

9. This was definitely shown in patients with liver disease herein presented.

10. Filter paper electrophoresis should be more available to the clinician.

## Acknowledgment

We wish to express our gratitude to Dr. James M. Winfield, Professor of Surgery, for the surgical patients; to the Residents in Medicine and Surgery for

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# ULCERATIVE COLITIS IN A SOUTHERN GENERAL HOSPITAL AND A SOUTHERN INDUSTRIAL-RURAL AREA*

## A Concept of Etiology and an Attempt at a Geography of the Disease

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and

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It has been stated that ulcerative colitis is an uncommon disease. In fact no single observer, with the exception of those working in large clinics and hospitals or those with a referred type of practice in gastroenterology, can accumulate a large series of cases. Because of the usual seriousness of the disease most of these cases end up under treatment in large clinics or hospitals and consequently it has been difficult to obtain statistics on the true incidence of the disease in general practice. There is a further clinical impression with which we concur, that ulcerative colitis is a rare disease in the Southern United States. Bockus[1] has stated that it seems less prevalent in warmer climates of the United States than in the northern sections. This, however, would again appear to be a clinical impression as no statistics are quoted. Spriggs[2] has reported an incidence of five per thousand hospital admissions and Kantor[3] nine per thousand hospital admissions. A few years ago Jones[4], at one of our sectional meetings, presented statistics on the incidence in the New Orleans area. These suggest that the prevalence of ulcerative colitis indeed may be less in this area than in more northern latitudes. In reviewing Jones' figures it was interesting to note that the rate per thousand admissions at Touro Infirmary in New Orleans was more than three times that of the incidence at Charity Hospital in the same city. Those familiar with the patient population of the two hospitals will recognize that Touro Infirmary is, for the most part, a private institution dealing with a more selective patient group and certainly one of higher socioeconomic status than the Charity Hospital group. Figures for the Veterans Administration Facility in New Orleans were intermediate between the two other hospitals.

Since practicing in Alabama we have been impressed by the paucity of cases in Birmingham and especially in the adjacent city of Bessemer. The purpose therefore, of this paper is threefold: 1. To determine the incidence of this disease in a Southern General Hospital (Birmingham Baptist Hospital) whose patient population is local; (that is a very small percentage of patients are re-

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ferred in from elsewhere in the state) and whose staff is comprised of at least 50 per cent general practitioners. The area served is made up largely of industrial workers of the middle class. 2. To calculate the incidence of the disease in a southern community, namely, Bessemer, Ala. 3. To offer an explanation as to why there is less ulcerative colitis in the Southern United States and especially in this area, if indeed this be the case. It should be pointed out that in referring to ulcerative colitis we are referring solely to the type which Bargen has classified as type I, i.e. with typical changes in the rectum as noted on proctoscopy, with upward progression, and manifested clinically by frequent stools or discharges mixed with pus, mucus, and blood. Regional colitis and the infectious types have been purposely omitted from this discussion.

In order to answer the first question, namely the incidence of the disease in a southern general hospital, all cases with this diagnosis at Birmingham Baptist Hospital between the years of 1951 and 1957 inclusive were reviewed. Between this period there were a total of 35 proven cases or a rate of 0.60 per thousand admissions. If we include 10 additional cases which were probably ulcerative colitis a maximum rate of 0.77 per thousand admissions is obtained. The breakdown in sexes revealed four males and 22 females. All were white. Total hospital admissions during this period were 57,576, exclusive of newborns. As you can see this is essentially similar to the average figure cited by Jones in the New Orleans area. Because of the character of the patient population we feel it is apt to be a close approximation of the incidence of the disease in this area. It is of interest that 20 additional charts were reviewed which had been coded out by the attending physician as ulcerative colitis but which obviously represented some other entity such as spastic colon, amebic colitis, etc. This would suggest the unfamiliarity of the average practicing physician in this area with the disease.

Bargen[5] has suggested that the reason for this low incidence of cases in the Southern United States is the relative infrequency of upper respiratory infections. It is of note that the winter of 1957-58 was the most severe in this area in many years. The number of cases of pneumonia and other infections of the respiratory tract admitted to the hospital and seen in practice made a tremendous increase—without affecting the number of ulcerative colitis admissions.

In contrast to Texter's statement[6] that ulcerative colitis is a serious disease, the majority of the cases seen here were mild. There has been no mortality; no cases of "acute" ulcerative colitis have been seen; and only two have required surgical procedures. One of these was an exploratory laparotomy and ileostomy for what appeared to be the most severe case of the group. The second was an incision and drainage of a perirectal abscess. There have been no other complications in this particular group.

Estimating the incidence of the disease in relation to the total population of a southern city was a somewhat more difficult task. It should be pointed out

that the population of the Bessemer area is estimated at 76,066* and is comprised of industrial workers, miners, and only a small percentage of "white collar" workers. Negroes make up approximately 20 per cent of the population. Rural residents constitute over 50 per cent of those who seek medical care in the city. Income varies from middle class to the lowest groups. Bessemer physicians serve not only the city proper but the surrounding rural area corresponding to the shopping and trade area, and served by the Bessemer Post Office. Because rural residents use a Bessemer address, it was necessary to extend this survey to the surrounding area and not just the city proper.

One of us has been in practice in Bessemer since 1952 and has had an unusual opportunity to arrive at some statistics in this regard. For a number of years as the only internist in this area a fair proportion of the difficult medical problems have been referred to our clinic. We have been impressed that from a total clinic enrollment of almost 19,000 patients during this period only *three* patients with ulcerative colitis have been seen and all of these have been extremely mild. Each one at the present time is known to be in a state of remission. A second internist entered practice in Bessemer in 1954 with a group of six general practitioners. His total experience has been one case, a college student. Since this group owns one of Bessemer's two hospitals this is likewise the experience of one hospital. At the second hospital, only two cases have been seen. Many difficult problems have been referred to nearby Birmingham for specialist care by Bessemer physicians over the years. Consequently it was felt that a survey of all internists in the Birmingham area could be made in an effort to determine how many referred cases from the Bessemer area each of these had seen. A questionnaire was sent in June 1958 to each Birmingham internist, being careful to specify that he list only cases seen from the Bessemer area. Geographically and practically this is not hard to do. From a total of 62 who were polled, replies were received from 54. From this entire group only 11 additional cases were uncovered, making a total of only 17 cases for the area since 1952. Based on the closest possible estimate of the population of Bessemer and adjacent area an estimate of the prevalence of the disease was calculated as 0.22 cases/1,000 residents. This is a lower rate than that for hospital admissions, both here and in New Orleans.

It is of interest that one of us after more than ten years of psychiatric practice in Birmingham has had only 3 patients referred with a diagnosis of ulcerative colitis. This is in marked contrast with the experience of one of our colleagues in Baltimore, Maryland whose practice consists of a considerable percentage of these patients. It would thus appear that the disease is: 1. uncommon in this area and 2. in our experience generally mild.

The next question which naturally arose is this: "if ulcerative colitis is less common in the Southern United States, why should this be so"? As Engel[7] has

*Based on 1950 census and corrected for rate of growth of Jefferson County, Ala.

pointed out in his monumental review there is no proof of any etiologic factor in ulcerative colitis. Nevertheless the concensus of opinion among those treating the disease today, especially as a result of the contributions of modern psychiatric research, would be to classify it among the group of so-called psychosomatic disorders. Rome[8] has gone so far indeed as to call the disease a "parapsychosis". It is very well recognized that ulcerative colitis is a disease of a particular personality type. These personality characteristics, behavioral patterns and the relationship between periods of emotional stress and the onset and exacerbation of symptoms in patients having ulcerative colitis have been well established. (Engle[7], Daniels[9] and Wittkower[10]).

With the above in mind, should not the disease be as common in the Southern as in the Northern climes of the United States? We think not. It has long been an accepted axiom that people react to stress in a manner acceptable in their own milieu. For instance the problems of "shell shock" or various types of conversion hysteria were common in World War I. Gradually down through the years less and less conversion hysteria has been seen, especially in the large metropolitan areas, probably because these illnesses have become socially unacceptable. In the same period more and more so-called psychosomatic illnesses such as hypertension and peptic ulcer have developed. "Shell shock" was an almost unknown entity in World War II, being replaced by "combat fatigue" and various types of acute anxiety reactions. When a patient with a complete hysterical paralysis of an upper extremity presented at the department of Psychiatry at the Mayo Clinic in 1948, one of the consultants remarked that she was the first such problem seen in that department in several years. It was of interest that this patient came from a remote section of Utah. While ulcerative colitis is rare in Alabama, it is of interest that one still sees gross hysterical manifestations frequently in the practice of internal medicine. During a six months period in 1958 all patients seen with such obvious hysterical manifestations as hysterical blindness were tabulated. Twelve such cases were seen. During the same period 40 patients presented with one of the various manifestations of the hyperventilation syndrome, all on an emotional basis. One is frequently called by a family in panic to treat a relative for a "stroke", "heart attack", blackout spell, or the like only to find the symptoms due to hyperventilation. This is seen in all age groups.

The majority of such patients live in farming or rural areas outside of Bessemer and Birmingham proper. Many of them have never been away from Alabama or this area. One is impressed by their more naive and unsophisticated approach to life as compared with our more blasé, if I may use the term, fellow countrymen in the north and east. Further, although no statistics have been kept on the matter, the prevalence of mild depressions in the practice of internal medicine is quite common. Although no statistics are available, from the incidental discussion of psychiatric problems between psychiatrists of the north, east, and south and the interchange of impressions, it appears that hysterical

conversion manifestations and depressions occur more frequently in the south than in the north. Anxiety reactions are essentially equally distributed. Emotionally induced asthma as well as the other more sophisticated psychophysiological reactions are more frequent in the north and east. This is likewise true of the problem of alcoholism. The more primitive or simple hysterical conversion reactions are seen more frequently in this area, the most common being aphonia, and next in order the anesthesias, paralyses, convulsions, blindness, deafness, etc. The symptoms represent symbolically an attempt to resolve a neurotic conflict. The reason for the greater frequency of depressions in the south is possibly the importance of the church, not only in the spiritual but in the social life of the individual. These customs and attitudes tend to develop a more rigid super-ego. In certain individuals who fail to successfully resolve their conflicts, the self punitive attitude of the super-ego precipitates a depressive reaction. It might also be pointed out that strong prohibitions on the part of certain church groups towards alcoholism undoubtedly play an important role in the lesser incidence of the latter disease.

Engel[7], in a study of 39 patients and a review of 700 from the literature found an impressive consistency of personality structure, long antedating the colitis. They are dependent individuals with restricted relationship with other people. A high percentage have a compulsive obsessive personality and are neat, orderly conformists with rigid attitudes toward morality and standards of behavior. They are patients with a complex neurosis and do not show overt psychoneurotic reactions of the complaining variety and as a matter of fact, the neurosis seldom creates a symptomatic problem. Hostility is a significant feature and is usually well submerged under an exterior of submissiveness. Sloan, Bargen and Gage[11] in a review of 2,000 patients with ulcerative colitis state that the generalization that neurotic problems must be a significant etiological factor does not seem to be warranted by their studies and that they were not impressed with the neuroticism of the patients. This is an important thing to bear in mind. These patients are not overt psychoneurotics of the complaining variety, in that the hostility, which is the major characteristic of the patient is usually well submerged under an exterior of submissiveness, hence the usual anxiety symptoms and tensions may be difficult to detect.

The individual, a group creature, is dependent for approval and sustenance on others and at the same time is threatened by a fear he might not live up to the expectations of those around him. The diverse stimuli, capable of producing different protective reaction patterns, is frequently determined by the social milieu of the individual. Ruesch[12] points out that American society is not distributed evenly from poor to wealthy, from successful to unsuccessful but that the population tends to cluster in groups, which are called social classes. The industrial workers, for example, have associations, beliefs and attitudes different from those of middle class people who live near the country clubs. The latter, in turn, have different attitudes from millionaires whose wealth has been passed

on from several generations. People of the working class for example are more exposed to industrial hazards than the middle class "white collar worker", but psychosomatic conditions and chronic illness seem to concentrate around the middle class. It is known that people with chronic disease and psychological invalidism have many characteristics of the middle class, they are law abiding and their repressive tendencies are great. The field of awareness is limited and they have difficulty in expressing anger and managing tension. In the industrial group of workers, on the other hand, we see overt psychoneurotic reactions and expressions of anger and conversion mechanisms. This social class reaction is pointed out as a strong possibility for the relative infrequency of patients with ulcerative colitis in our industrial and rural community.

Frustration is psychologically expressed in anger and physically in terms of tension. In our country, there exists a premium on the need to excel and make good. This imposes an unusual stress and strain on the individual who feels the necessity to improve his condition rather than to enjoy his present status. Cultural changes play a major role in chronic disease. It is stated that one-half of the American population is in the process of cultural change. This involves readaptation and relearning new ways of living, attitudes, beliefs, and systems of values. This is particularly true in the large urban areas. In Bessemer and the surrounding rural areas, the cultural changes have been relatively less significant.

It would thus appear that the sum total of the cultural and socioeconomic factors in the area surveyed, directs reaction patterns into other channels than ulcerative colitis. It is entirely possible that in the future, the transformation from a primarily agricultural to a more balanced economy, the increase in per capita income and an over all change in the culture of the south, will change this picture and more of the sophisticated psychophysiological reactions will appear in this part of the country.

## Summary and Conclusions

1. A survey of the incidence of ulcerative colitis in a southern general hospital has been made between the years of 1951 and 1957. Likewise the incidence of the disease in a southern industrial community over a similar period has been estimated. This represents an attempt at establishing a geography of the disease.

2. It would appear that there are basic differences in emotional reactions in various parts of the country and types of neuroses seen in psychiatric practice. Cultural changes and social milieu play a major role in each individual's reaction to stress. In this area conversion reactions and depressions are more commonly seen. Alcoholism appears to be a less common problem than in the north and east. In the industrial and rural groups of this area it would seem that these forces frequently direct reaction patterns into other channels than ulcerative colitis. Thus, in substantiation of previous psychosomatic studies,

from the standpoint of both culture and epidemiology, the evidence would point to ulcerative colitis as a psychosomatic disorder.

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DISCUSSION

*Dr. Harold I. Lief (New Orleans, La.):*—I think we should feel indebted to Drs. McMahon and Morton for bringing an interesting number of facts and some interesting speculations to our attention. In addition, I think any paper which contributes ideas for further investigation is of value. I think that in a sense the paper has been obscured by bringing in certain features which aren't quite necessary. Nonetheless, the value of the paper seems to me to be very definite.

Let's take a closer look at the points made by the authors.

They say that ulcerative colitis, according to their statistics, is both rare and mild in the South. I am not going to spend much time on statistical analyses. I am not an expert at that, but I would like to say that empirically my observations and those of colleagues whom I have approached about this problem agree with the observations of the authors.

In Charity Hospital, for example, we find that ulcerative colitis does occur more rarely than it does in the North, and it seems to be definitely milder.

I had the opportunity, when I was on the staff at Presbyterian Hospital some ten years ago, to engage in a study of ulcerative colitis, and I would say

from my experience it was much more common in that hospital than it is in Charity Hospital.

There are some points that have to be considered more carefully. For example, we see relatively few cases among Negroes in Charity Hospital. Is this racial or is this a class-oriented feature? In any case, the percentage of Negroes may offset the statistics. In Dr. McMahon's statistics there were only 20 per cent Negroes in the Bessemer area, so we can exclude this as a basis for his low percentage of ulcerative colitis. It may be more important in a region such as this, in which we have over 50 per cent Negroes in the area and certainly over that in terms of admissions to Charity Hospital.

All right, let us accept this as a fact. Where do we go from here? Their speculation is that this is based on class, a social class relationship. They use as one of the bases for their speculation the well-known fact that there has been a change in the nature of certain emotional and mental symptoms over time. For example, there has been a decrease in the incidence of conversion hysteria symptoms and an increase in psychosomatic illness over a period of time. As a further illustration of this, we know that peptic ulcer was seven times more frequent in English soldiers in World War II than it was in World War I. The same is true of the civilian population, so there is tangential evidence that social change can produce change in the nature of symptomatology.

I think, however, the authors obscured their arguments somewhat when they brought in the matter of alcoholism and depression. I don't see that a discussion of these entities helped to clarify the situation. They state that depression is high and alcoholism is low in the Bessemer area.

Now, we know that actually depression and alcoholism generally go together statistically. One can take a look at the Scandinavian countries, for example, which have about the highest incidence of alcoholism and the highest incidence of suicide in the world.

I am willing to buy the statement that hysterical symptoms are greater in the Bessemer area than in general in the South, but I am not willing to buy the statement that depressive reactions are higher and alcoholism is lower.

Another thing is that we know that depressive reactions and psychosomatic illnesses tend to cluster. Where you generally get a high incidence of depressive reactions you likewise get a high incidence of psychosomatic reactions.

Apparently the authors believe that in general there is a lower incidence of psychosomatic reactions in their area. Apparently it isn't only ulcerative colitis that is reduced. This would warrant further investigation.

Now, when we take the main point, that this is related to the social class, I think we must look at this a little more carefully. If it is a matter of class, can we then investigate further to see whether it is a matter of intelligence, literacy,

values and standards, the level of aspiration, the degree of frustration, motivational conflicts, etc. Hinkle and Wolff, for example, in their study in the New York area, showed that job satisfaction is the most important factor in differentiating the well from the ill group. We would like to know much more about these factors before we can really see clearly whether this is actually a class-related feature.

In a survey that has been done here in New Orleans in which I participated, we discovered that one must study a smaller unit, the family, in order to get some of these answers. Class divisions are generally too vague and too confusing. What do you do with a chap who has a Master's degree from Yale and works as a waiter, or with a boxer who never went beyond the third grade and has earned over a million dollars?

There may be other etiological factors that are more important than class reaction in the low incidence of ulcerative colitis in the South. For example, one could have assigned the same reasoning to pellagra some years ago. This could have been seen as a class-limited illness. The class is only indirectly associated with pellagra through a steady diet of red beans and rice.

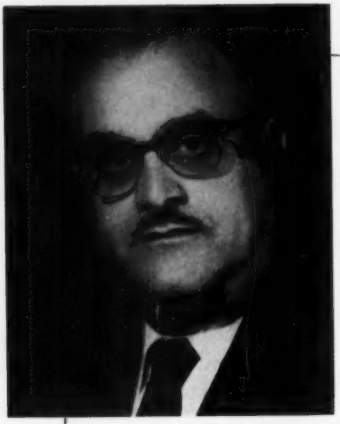
Nevertheless, I think these authors deserve a lot of credit for bringing this to our attention.

There have been a number of studies recently on the epidemiology of mental illness. With regard to the incidence among social classes, this seems to be a fruitful area for research. Steigmann, for example, (in *The Biology of the Negro* by J. H. Lewis, University of Chicago, 1952) reported that peptic ulcer was greatly increased in Southern Negroes who had migrated North after they had spent about six years in the North.

This, I think, leads us to say that we should study not only social classes in one area, from an epidemiological viewpoint, but comparable social classes in other areas of the country. Still more interesting would be to study migrants for changes in patterns of disease. Above all, we should study selected families. A great deal can be learned from intensive medical and psychiatric study of families in conjunction with these epidemiological methods.

Finally, the authors suggest that the Bessemer area has been relatively stable from a cultural point of view. Another possibility for further research suggests itself. Why not study a nearby area, say within two hundred miles, where there has been significant social and cultural change. This might measure the impact of social and cultural change on patterns of illness, including ulcerative colitis.

I feel that the paper has been significant if it has brought out a single important fact about ulcerative colitis. I think it has. The identification and elucidation of any one condition represents an important advance in the understanding of the disease, even if it does not explain the pathogenesis or establish the etiology.



## *President's Message*

### Radiation Hazards in Gastroenterology

The other day at the medical school one of the attendings asked me, "Would you do a complete gastrointestinal series on a young girl in view of the dangers of radiation, since the patient's parents are aware of the hazards as discussed in the press?"

I answered yes, there are hazards yet no misconception should prevent a patient from receiving the benefits of modern medical care possible in a well done, necessary x-ray examination with the least amount of danger. This may mean little or no fluoroscopy and no unnecessary repeat films.

We as physicians have the responsibility of keeping additional gonadal radiation as low as possible, since geneticists have shown that the radiation dosage to the gonads should not be further increased in the future, because already the medical use of radiation in this country has equalled the amount generally received by background from natural sources. One who uses x-ray equipment should know how much radiation is being delivered to the body of the patient, especially to the gonadal region. The difference in bad and good technic, proper and improper filtrations may many times affect the dosage delivered to the reproductive organs. Is the diagnostic procedure necessary in the judgment of the attending physician yet not denying the patient all possible medical care? How often are unnecessary examinations ordered before a comprehensive study of the patient or already available films or other information is considered? Much can be done to reduce this hazard by the gastroenterologist and the radiologist, especially in the examination of the younger group, by a proper dark adaptation of the examiner's eye before fluoroscopy. Cutting down on the shutter opening and increasing the thickness of the filter and the wise use of film and cone, will greatly minimize x-ray exposure to the patient and operator as well.

In conclusion, if the examination in the young is necessary, it is worth being done well with modern equipment, proper technic and by the best qualified examiner with as little fluoroscopy as possible for best qualified examination.

Frank J. Borrelli

## NEWS NOTES

### College Committees

The following standing committees of the American College of Gastroenterology have been appointed for 1959 and the members will serve for the number of years shown after each name.

*Program Committee:*—Dr. George K. Wharton, Los Angeles, Calif., Chairman (1); Dr. Walter L. Mersheimer, Scarsdale, N. Y. (1); Dr. Dale W. Creek, Santa Barbara, Calif. (2); Dr. Julian A. Sterling, Philadelphia, Pa. (3); Dr. Stanley S. Sidenberg, Cleveland, Ohio (4); Dr. Lynn A. Ferguson, Grand Rapids, Mich., Secretary-General.

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The following Special Committees were appointed to serve for one year:

*Scientific Exhibit Committee:*—Dr. Lester M. Morrison, Los Angeles, Calif., Chairman; Dr. Joseph E. Walther, Indianapolis, Ind.; Dr. Max E. Moravec, Schenectady, N. Y.; Dr. Frederick Steigmann, Chicago, Ill.

*Membership Committee:*—Dr. Joseph Shaiken, Milwaukee, Wisc., Chairman; Dr. Milton J. Matzner, Brooklyn, N. Y., Dr. M. E. Steinberg, Portland, Oreg.

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### Fellowship Keys

Keys for *Fellows* of the American College of Gastroenterology have been authorized by the Board of Trustees. An illustration of the key is at the left.

These may be ordered from the headquarters office, 33 West 60th Street, New York 23, N. Y., at $10.00 each including federal tax and shipping charges.

The reverse side of the key will be engraved with your name and the date of your election to Fellowship. Send your order today.

## In Memoriam

We record with profound sorrow the passing of Dr. Louis B. Goldman, Chicago, Ill., Associate Fellow and Dr. Arthur L. Holland, New York, N. Y., Honorary Fellow of the American College of Gastroenterology. We extend our deepest sympathies to the bereaved families.


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[1] *American Journal of Gastroenterology* 28:439, 1957.

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## STOMACH

**LONG-TERM RESULTS OF VAGOTOMY AND GASTROENTEROSTOMY IN CHRONIC DUODENAL ULCERATION: Harold Burge and E. J. Pick. Brit. M. J. 5071:613 (15 Mar.), 1958.**

The authors conclude that vagal resection with gastroenterostomy is the operation of choice in either sex at any age when surgery is indicated for chronic duodenal ulceration. In 301 cases with vagal resection followed for at least seven years, they found that the mortality rate was nil in a personal series of 100 cases and they quote from Crile (445 cases) with a 0.4 per cent mortality and Hoerr with a 0.5 per cent mortality rate. Gastrectomy, in the most skilled hands, carries a 1-2 per cent mortality. The morbidity in the vagal resection cases was minimal with none of the serious complications such as duodenal stump leakage or hemorrhage. Nutritional state impairment as measured by weight loss occurred in 47 per cent of gastrectomized cases as against 10 per cent in vagal resections. No change in the ability to work occurred in the cases of vagus resection whereas it was unusual for a patient with a gastric resection to return to heavy work. Anemia was a common condition post-gastrectomy but did not occur after vagal resection. Diarrhea, a commonly mentioned disadvantage after vagotomy, occurred in only 30 per cent of cases and consisted of bouts of diarrhea of 1-3 days' duration every 1-3 months. These episodes were not disabling. A similar type of bowel disturbance occurred in 20 per cent of post-gastrectomy cases! Postcibal symptoms including dumping were considerably less than in gastrectomy cases. Recurrence rate of ulceration in the vagectomy series was 4.25 per cent (eight-year follow-up) versus reported recurrence rates in gastrectomy series of 2-6 per cent. The authors feel that the figure of 4.25 per cent included many cases of incomplete vagal resections. They found that a positive insulin test was present in every case of recurrent ulceration. Some improvement in recurrence rates may be expected with the employment of a new test for the completeness of nerve section during surgery.

Jules D. Gordon

**RETROPERITONEAL DUODENAL RUPTURE: Brit. M. J. 5069:505 (1 Mar.), 1958.**

Although not often reported rupture of the duodenum is estimated to account for 10 per cent of all gastrointestinal ruptures. Most duodenal ruptures affect the second and third portions of the loop, but only 25 per cent perforate retroperitoneally.

A single flat film of the abdomen showing an air bubble about the kidney or its retroperitoneal equivalent is said to be most helpful.

Early surgical closure without narrowing the duodenal lumen is imperative. This postoperative narrowing is so common that the authors outline in detail several precautions that have to be taken. In addition other postoperative complications are common including infections, stenoses and fistula formation of adajacent organs.

A detailed case report is given since presently the mortality rates of all gastrointestinal surgery is steadily decreasing.

A. M. Susinno

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**POSTGASTRECTOMY HEMORRHAGE: Richard B. Phillips and Wesley A. Childs. Am. J. Surg. 95:411 (Mar.), 1958.**

Hemorrhage following gastric resection is a serious but little mentioned complication. The writers report their clinical experience in a series of 123 gastrectomies performed since 1948. Postgastrectomy hemorrhage in this report is defined as any bleeding in the postoperative course which requires 500 c.c. or more of blood replacement. The mortality and over all morbidity rates are similar to those reported by others.

This complication was the second most frequently encountered and was exceeded only by superficial wound infections. Hemorrhage was the contributing factor in three of the seven deaths and necessitated three of the 13 secondary operations. It is generally reported that postgastrectomy hemorrhages occur between the first and fifth postoperative day, but it may occur at any time, as late as the 14th day and the over all incidence ranges between 1 and 3 per cent.

Carl J. DePrizio

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**PEPTIC ULCER AS A SURGICAL PROBLEM: Claude J. Hunt. Am. J. Surg. 95:401 (Mar.), 1958.**

The author reviews the history of the progressive changes in the treatment of peptic ulcer. At the present time, suffice it to say that no longer is gastroenterostomy or pyloroplasty an operation of contention, but gastric resection with or without vagotomy is the controversial issue. The procedure of partial gastric resection with or without vagotomy gives the lowest incidence of recurrence and the minimum of undesirable postoperative sequela.

Perforated peptic ulcer is a surgical emergency. Therefore, surgical exploration, rather than gastric drainage and a medical regimen should be undertaken. Gastric ulcers which perforate should usually be resected at the time of exploration, because of the uncertainty of the histological nature of the lesion; whereas, perforation of a duodenal ulcer may require simple closure and some certain conditions may even indicate subtotal gastric resection, especially if there are signs of obstruction and bleeding.

Massive hemorrhage from ulcer is a major complication of peptic ulcer and too often there is a tendency to defer operation until vascular collapse occurs. The writer believes that if a patient's circulatory balance is not restored and maintained after receiving four to five units of blood, operation should be instituted at once.

For chronic pyloric obstruction that does not improve after two or three trials with adequate medical management, gastric resection should be advised.

Ulcers high on the lesser curvature should be treated with fundusectomy with esophagogastrostomy, if the high resection cannot be accompanied by a segment of the fundus remaining as a food pouch.

Gastrojejunal ulcer, after gastroenterostomy, should be treated by a subtotal gastric resection with or without vagotomy. It is unwise to leave an ulcer when it is possible to remove it, regardless of location. Many ulcers may not heal or remain healed

and continue to give symptoms and often bleed.

The writer has not had too much difficulty with the dumping syndrome and he performs the Hofmeister anticolic type of anastomosis and buttresses the distal limb of the jejunum against the closed upper third of the lesser curvature of the residual stomach. This retards the emptying and is well tolerated by the patient.

Colonic replacement in surgery of the stomach has an obvious increased mortality rate due to prolonged procedure and multiple anastomoses. It is inferior to high gastrectomy with or without vagotomy. Intestinal segments to replace a portion of the stomach are too often susceptible to ulceration and the lower the intestinal tract the segment is taken from, the greater the susceptibility to ulceration.

CARL J. DEPRIZIO

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**THE BELCHER GASTRECTOMY FOR PEPTIC ULCER: D. G. MacQueen. Canad. M. A. J. 78:320 (1 Mar.), 1958.**

The author compares the end results in 1½ to 5 years follow-up of 100 cases of peptic ulcer patients who have had a Belcher type gastrectomy with those of 100 patients having the Hofmeister-Polya type.

In the Belcher operation the distal 3" of the newly formed stomach is tubed to the same caliber of the duodenum which has been sectioned, distal to the ulcer and then anastomosed to it. This operation was primarily intended to overcome 1. rapid gastric emptying time 2. afferent loop dilatation and 3. lack of suspension of the gastric remnant to prevent the mechanical drag on the remaining stomach and esophagus.

In the Belcher group, the weight loss (5 lbs. plus) occurred in 4 per cent as compared with 70 per cent in the Hofmeister-Polya; dumping syndrome 3 per cent as compared with 25 per cent in the latter; rapid gastric emptying time 4 per cent as compared with 54 per cent in the latter; recurrence of 2 per cent in the Belcher type as compared with none in the Hofmeister-Polya. The Hgb. values ranged from 12.5 to 18.3 gm. per cent in the Belcher type.

The author attributes the favorable results to the establishment of a more nearly normal continuity in the digestive tract, so that certain essential absorptive functions (such as iron absorption) of the duodenum are better preserved. The reduction of the gastric emptying time is attributed to the resection of the lesser curvature and the tubular form of the distal end of the gastric remnant. Because of the slow emptying these cases require a longer period before they regain full gastric capacity.

SAUL A. SCHWARTZ

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**THE ACUTE ABDOMEN DUE TO TRAUMA: William M. McMillan. Illinois M. J. 113:91 (Mar.), 1958.**

The author discusses penetrating and nonpenetrating wounds of the abdomen resulting from abdominal trauma. The most frequent nonpenetrating wound is injury to the right lobe of the liver. Penetrating abdominal wounds require exploration but nonpenetrating wounds raise the question when to operate and when to leave the patient alone. If diagnosis is in doubt exploratory operation should be performed.

Urgent associated injuries, such as wounds of the head, neck and extremities should be cared for first. Shock should be treated, transfusions administered and the patient should not be rushed to surgery. Blood counts, and flat films of the abdomen are of great value.

Once surgery is undertaken thorough exploration must be performed. How to control massive hemorrhage intraabdominally is carefully described. Careful attention should be paid to stomach and duodenum to determine injuries.

Treatment of bowel wounds, ruptured spleen, ruptured liver, ruptured kidney and injuries to diaphragm are also carefully gone into. Postoperative management and antibiotic therapy is described.

ABRAHAM BERNSTEIN

## INTESTINES

**A NEW ACUTE GASTROENTERITIS FOUND IN THE SAGAMIHARA NATIONAL HOSPITAL: Toshio Goto et al. Yokohama Med. Bull. 8:166 (June), 1957.**

A new gastroenteritis, with a well worked up epidemilogy and the causative factor in food, particularly scrambled egg soup, is presented with details.

The clinical findings are those of the incubation period averaging about nine days with an unusual abrupt onset of diarrhea, abdominal cramps, etc. The clinical course usually takes several days, but no more than two months. The fever lasts only two or three days and is over in less time in a majority of the cases. The sedimentation rate is moderately accelerated on the third to the fifth day and returns to normal by the tenth day. The blood pressure is that of a slight leukopenia from the second to the seventh day. This new acute gastroenteritis is differentiated from the epidemic gastroenteritis by the following points; a. longer incubation period, five to six days against two to three days, b. higher fever of 38.5° against 32.2° C. The innoculation experiment, however, failed to determine the origin of the disease, although a virus etiology is suspected.

VINCENT J. GALANTE

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**ROENTGEN DIAGNOSIS IN THE ACUTE ABDOMEN: Roger A. Harvey. J. Lancet 77:49 (Feb.), 1957.**

The roentgen examination of the acute abdomen can offer a great deal of diagnostic information if adequate examination is possible and the right combination of technics is used. In particular, incipient intestinal obstruction can be seen as well as peritoneal irritation reflected in the bowel pattern. Stones in both the gallbladder and renal areas seen by x-ray can be a valuable aid in arriving at a diagnosis of abdominal complaints. Vascular lesions such as aneurysms and mesenteric vascular occlusion can be suspected by adequate x-ray studies. The author calls attention to the fact that the roentgenologist can assist the surgeon in many instances both before and after surgery.

BERNARD J. FICARRA

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**MECKEL'S DIVERTICULUM WITH MASSIVE HEMORRHAGE: Robert L. Gilbert and Matt A. McGarty. Wisconsin M. J. 56:317 (July), 1957.**

Meckel's diverticulum with massive hemorrhage is fairly frequent in young patients. However, it is quite unusual in elderly patients. The authors report a case of a 67-year old male who was admitted because of massive gastrointestinal hemorrhage. He was eventually subjected to surgery with an established preoperative diagnosis of diverticulosis and diverticulitis of the sigmoid colon. A primary resection and end-to-end anastomosis were performed. However, with blood running into three extremities simultaneously, the patient remained in shock. Because of this feature further exploration was carried out, and a Meckel's diverticulum was discovered. The resected specimen had islands of gastric mucosa and pancreatic tissue, and a bleeding site in the base of a peptic ulcer in the diverticulum was identified.

CHESTER S. SVIGALS

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**REGIONAL (SEGMENTAL) CHRONIC ULCERATIVE COLITIS: Michael W. Shutkin. Wisconsin M. J. 56:333 (Aug.), 1957.**

The term "regional (segmental) colitis", refers to an inflammatory disease of unknown origin involving one or more segments of the large intestine. It has been suggested that the localized lesion is more closely related to regional enteritis than to ulcerative colitis. Secondary involvement of the terminal ileum occurs frequently. Two cases of segmental ulcerative colitis are reported, affecting a mother and daughter.

BERNARD STERN

**DIVERTICULITIS OF THE JEJUNUM: Frederick M. Graham. Northwest Med. 56:1318 (Nov.), 1957.**

This case report concerns a ruptured jejunal diverticulum which was operated with a preoperative diagnosis of ruptured peptic ulcer. The literature since 1938 records only six cases of acute jejunal diverticulitis with three perforations and one death. The most common preoperative diagnosis was that of perforated peptic ulcer. Gastrointestinal bleeding has been an occasional symptom but only a very small percentage could be said unequivocally to have symptoms directly attributed to their diverticula. Without question, some diverticula do cause chronic digestive disturbances, a conclusion which was borne out by this case reported.

JOHN E. COX

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**NEONATAL GASTROINTESTINAL TRACT PERFORATIONS: Fletcher A. Miller. J. Lancet 77:439 (Nov.), 1957.**

The authors report five newborn infants with gastrointestinal tract perforations. Four of the five patients survived. Attention is called to symptoms which should lead to suspicion of perforation. These include pronounced abdominal distention, respiratory distress, vomiting of bile stained material and often absence of peristalsis. Evidence of free air in the abdomen or stippled calcification on x-ray should cause one to consider meconium peritonitis.

Bile obstruction is the usual cause with other unproven etiologies including obstetrical trauma, localized bowel wall defects, and localized inflammatory processes. The history of one of the patients reported suggests the possibility of gastric perforation secondary to gastric intubation.

Contrast x-ray studies are to be avoided. Emergency surgery is the treatment.

BERNARD FARFEL

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**EXPERIENCES WITH THE "SECOND-LOOK" PROCEDURE IN THE MANAGEMENT OF CANCER OF THE COLON AND RECTUM: Stuart W. Arheiger, Conrad B. Jenson and Owen H. Wangensteen. J. Lancet 77:412 (Nov.), 1957.**

Second-look operations have been done on patients who had gastric, colic or rectal cancers with lymph node metastases. Second-look operations are done at 6-month intervals until a final negative for any suspicious tissue results, unless the situation is an inoperable one. It was found that approximately ⅓ of patients with resectable visceral cancers had metastases to the regional lymph nodes. Three illustrations are given including a patient who had 6 operations before no residual cancer was found.

Ninety-six patients with lymph node positive cancer of the rectum or colon are reported. Fifty-one per cent had residual cancer at the second operation. The operative mortality was zero for those who had negative explorations. The mortality in the other cases was related to the extensiveness of the approach to extirpate residual cancer.

Further results of the study have shown routes of spread particularly relating to early residual cancer. The authors advocate regular dissection of the iliac, hypogastric, preaortic, and inferior *vena cava* nodes in the treatment of cancer of the colon and rectum. Favorable results appeared to follow the second-look approach. There is insufficient information at this time to formulate accurate statistics.

BERNARD FARFEL

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**EARLY DETECTION OF CANCER—A NINE-YEAR STUDY: W. Albert Sullivan, Jr. and John B. Lunseth. J. Lancet 77:408 (Nov.), 1957.**

Keeping in mind the increasing incidence of cancer and its climb to the second leading cause of death, the Cancer Detection Center was organized nine years ago. The age limitations were imposed at 45 years and over for women and 50 years and over for men. Patients were picked for lack of ordinary symptoms. A routine for cancer detection was set up. Patients examined on an annual basis totaled 8,229, the average

patient having had three examinations. Of these patients, 2.7 per cent have been found to have cancer. Early diagnosis of lesions of the urinary tract, pancreas and biliary tract is difficult. Survival rate in the asymptomatic group is 77.9 per cent as contrasted with 53.2 per cent in the symptomatic group. In lesions of the gastrointestinal tract, there is a 68 per cent survival rate in the entire group, a 76.9 per cent survival rate in the asymptomatic group contrasted with an over all survival rate for the country of 25 to 30 per cent.

BERNARD FARFEL

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**PROBLEMS IN DIAGNOSIS AND PRINCIPLES OF TREATMENT OF CANCER OF THE LARGE BOWEL: Leland S. McKittrick. Wisconsin M. J. 56:486 (Dec.), 1957.**

Thirty-one of 100 consecutive patients operated upon for cancer of the large bowel came too late for reasonable chances of cure. In each of these instances the important delay was due to failure of the physician to recognize the importance of the symptoms. Important factors involved in this delay are lack of correlation between symptoms and the final diagnosis; incomplete or inadequate examination; and overconfidence in the accuracy of x-ray examination. These factors are discussed in detail and the principles of the total operative management are outlined.

GLENN S. ROST

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**TORSION OF THE OMENTUM AND APPENDICES EPIPLOICAE CAUSING ACUTE ABDOMINAL PAIN: H. J. Till and John M. Cameron. J. M. A. Alabama 27:133 (Dec.), 1957.**

The authors report two cases of idiopathic torsion of the omentum with infarction and two cases of idiopathic torsion of the *appendices epiploicae* with infarction as a cause of acute abdominal pain. These conditions should be considered preoperatively in cases of acute abdominal pain and looked for at operation after the more common causes of abdominal pain are excluded. They are probably as frequently the cause of abdominal pain as Meckel's diverticulum and should be looked for in the same manner. If overlooked or maltreated, they may slough or possibly be absorbed with only an adhesion remaining. It has been suggested that these conditions may sometimes cause small-bowel obstruction due to adhesions in a patient who has had no previous operation. There have been several deaths reported in literature from both of these conditions.

JOHN M. MCMAHON

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**MALIGNANT TUMORS OF THE COLON AND RECTUM: R. W. Postlethwait and J. E. Adamson. Clin. Med. 4:1527 (Dec.), 1957.**

The authors review the statistics of a series of 1,023 patients with carcinoma of the colon or rectum seen at the Duke Hospital, during the period of 1930-1955. They report a 5-year survival rate of about 25 per cent and stress the need for early diagnosis. The majority of cases was seen in the 50-70 year age group, with male and female equally affected. The sigmoid and rectum accounted for 75 per cent of the cases and the cecum for 10 per cent. They list the premalignant lesions as familial polyposis of the colon, adenomas of the bowel which are multiple in 33 per cent. From reported surveys they had found a 5 per cent incidence of carcinoma in cases of cronic ulcerative colitis of 5-year duration.

The authors review methods of examination and discuss medical and surgical treatment.

SAUL A. SCHWARTZ

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**MANAGEMENT OF GERIATRIC CONSTIPATION: Eugene Coodley. Clin. Med. 4:1509 (Dec.), 1957.**

The author lists the types of constipation as acute and chronic; spastic in young, atonic in the old and rectal dyschezia with the failure of the defecation reflex, with

retention of feces in rectum. He attributes the causes in the geriatric patient to loss of interest in eating, faulty dietary habits, laxatives and enema habits, inactivity, endocrine dysfunction, use of ganglionic-blocking agents, iron, narcotics, amphetamine and antacids. Among the organic causes are diverticulosis, redundant colon, bowel tumors, mechanical or paralytic obstruction, megacolon and rectal disorders.

In discussing treatment, the author recommends the use of a roughage diet for the elderly patient with atonic constipation. He discusses the merits and disadvantages of various cathartics such as phenolphthalein, cascara, salines, hydrophilic colloids, emollients, dioctyl sodium sulfosuccinate.

He summarizes his experience with an agent containing bile salts, phenolphthalein, cascara and *oleoresin capsicum*, under the trade name of Veracolate, used in 55 patients in a sanitarium. After a 6-week course he found that 51 out of the 55 patients had satisfactory results not experienced with other medications.

SAUL A. SCHWARTZ

---

**DIGESTIVE CONDITIONS IN LA GRIPPE: E. Arias Vallejo, A. Barallobre and V. M. De Marcos. Rev. espan. enferm. ap. digest. 17:32, 1958.**

The writers study the involvement of the digestive system with reference to the latest epidemic in Madrid. They pay particular attention to gastric, intestinal and hepatic syndromes, brought about by virus infection and also by inappropriate management of the disease carried out by the patient himself without medical advice. The different types of influenzal gastroenteritis are described. They then deal with liver involvement, present in almost every patient, which usually runs a benign course. They review the fairly severe cases of icteric hepatitis in patients suffering from chronic liver disease (hepatitic or cirrhotic) occurring in the course of influenza.

The treatment of influenza with its accompaniment of hypertrophic gastritis, peptic ulcer and toxic hepatitis is inappropriate. Comment is made on postvaccinal encephalitis which is often associated with an obvious digestive syndrome.

Finally, they analyze the prophylaxis of digestive involvement in influenza and recommend suitable diets and treatment with gamma globulin, ascorbic acid, deproteinised liver extracts, Vitamin A and Vitamin B-complex. As antipyretic drugs they recommend pyramidon by oral or rectal route.

FRANZ J. LUST

---

**CARE OF THE PATIENT WITH A COLOSTOMY: William C. Bernstein. J. Lancet 78:16 (Jan.), 1958.**

Patients should never be taught to irrigate a colostomy first. They should be instructed to take tub baths as often as they desire and that a soft wash cloth can be used directly over the stoma for cleansing. Specific simple instructions should be given, and if irrigations are necessary, an asepto syringe, a catheter, and lubricant are all that is needed in the way of equipment.

If a patient can irrigate and empty his colon in a period of 30 to 45 minutes, and if he can remain clean for 24 to 48 hours, bowel function is being performed satisfactorily, and appliances are not necessary, and should be discouraged. If the bowel is emptied well, with or without irrigation, a small piece of gauze under an elastic abdominal support should be sufficient. However, some patients will insist on wearing a ring and plastic cover on a colostomy for their own self assurance. This point is not worth arguing about.

Patients are usually told to eat everything, and to omit foods which have a tendency to cause frequent loose movements or the formation of large amounts of gas. Restricting the diet in patients with colostomies is unnecessarily overemphasized. Group therapy in emotional and other psychiatric disturbances should be encouraged.

CARL DEPRIZIO

---

**DIVERTICULITIS OF THE COLON: M. M. Zinninger. Med. Times 86:158 (Feb.), 1958.**

Although diverticula of the colon are commonly present in persons over 40 years of age, they seldom cause trouble. For that reason, many physicians tend to disregard

them. It is the author's contention that the medical profession has been too prone to regard diverticula of the colon as of little importance, and that there has been a tendency to avoid operative intervention unless serious complications develop.

Among complications which can occur and which should be treated by surgical intervention are: acute and chronic inflammation, resulting fistula-formation, abscess-formation, perforation, partial or complete obstruction, hemorrhage, and inflammatory tumor to be confused with malignancy.

The author reviews in detail these syndromes, as regards to diagnostic criteria and technical details of surgical management.

H. J. Joseph

---

**VOLVULUS OF SMALL BOWEL DIAGNOSED PREOPERATIVELY: Erik Christensen. Brit. M. J. 5068:442 (22 Feb.), 1958.**

The author presents 6,892 collected cases of intestinal obstruction in which volvulus was the causative factor in 176, one-fifth of them involving the small bowel. He rightly stresses the difficulty of early diagnosis of this condition which when treated early is not of much consequence but when treated late carries a high mortality. Two case histories are presented which are rather illuminating.

D. P. Hall

---

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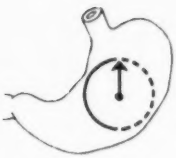

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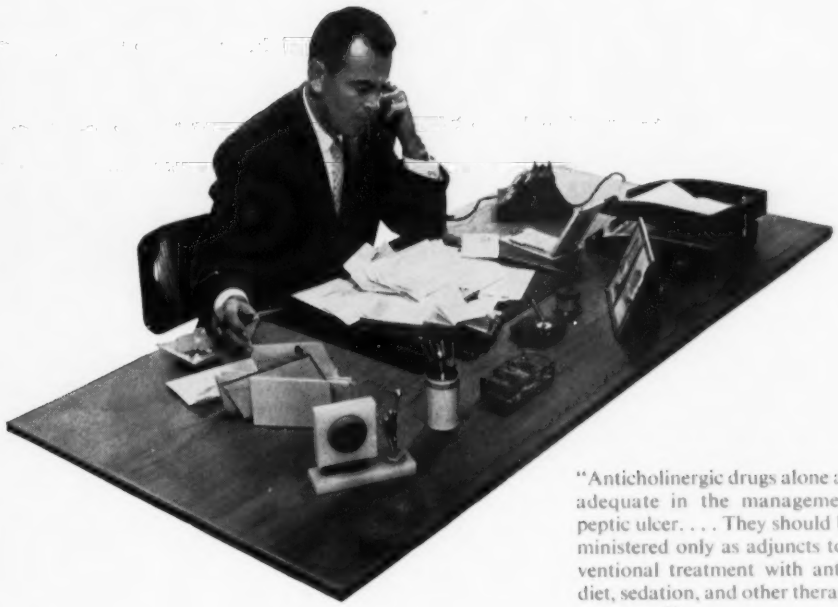

"Anticholinergic drugs alone are inadequate in the management of peptic ulcer. . . . They should be administered only as adjuncts to conventional treatment with antacids, diet, sedation, and other therapeutic measures."[1]

1. Kirsner, J.B., et al.: M. Clin. North America *41*:499 (March) 1957.

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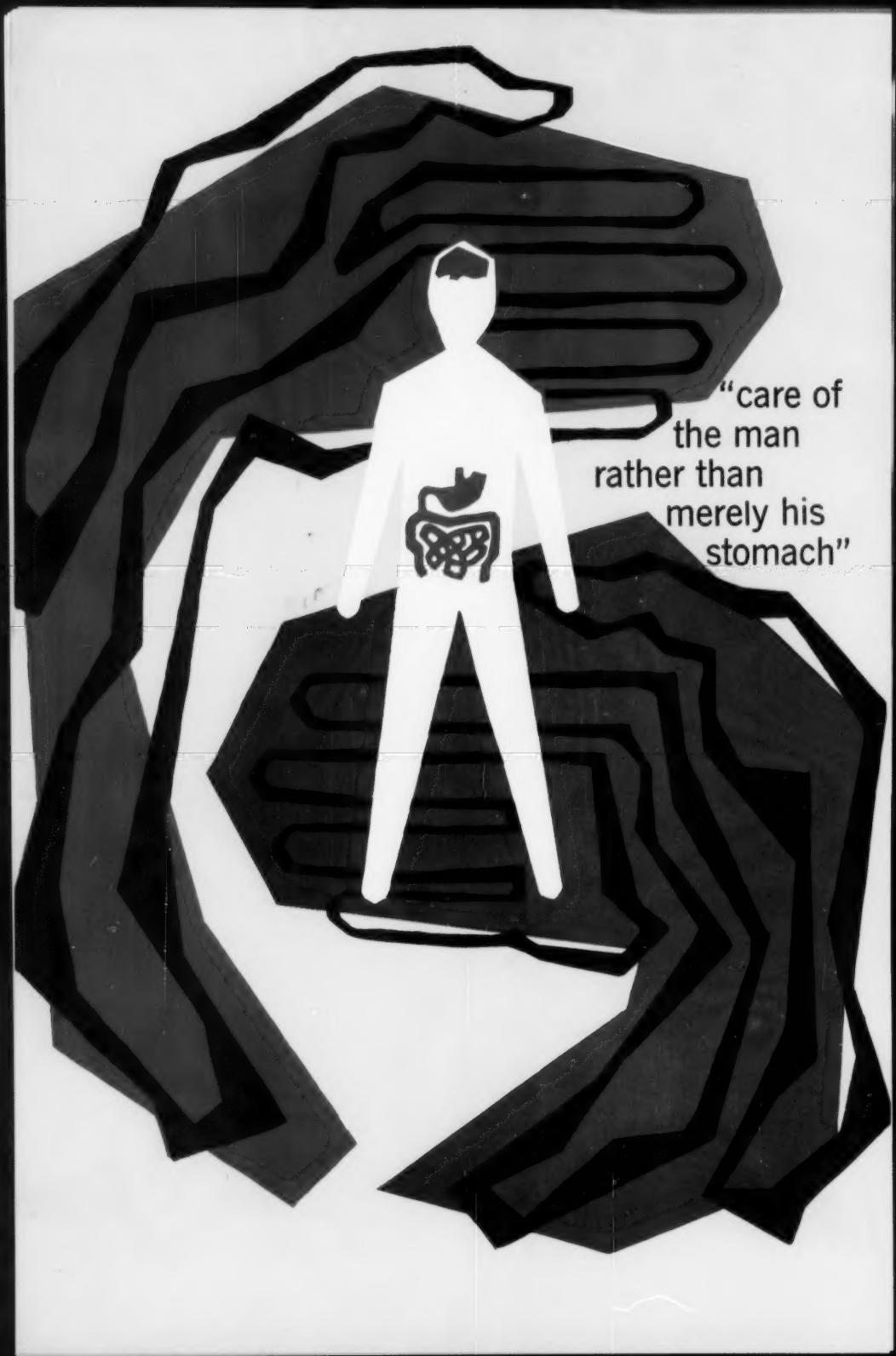
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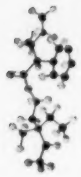
three-way mechanism of action  in one molecule

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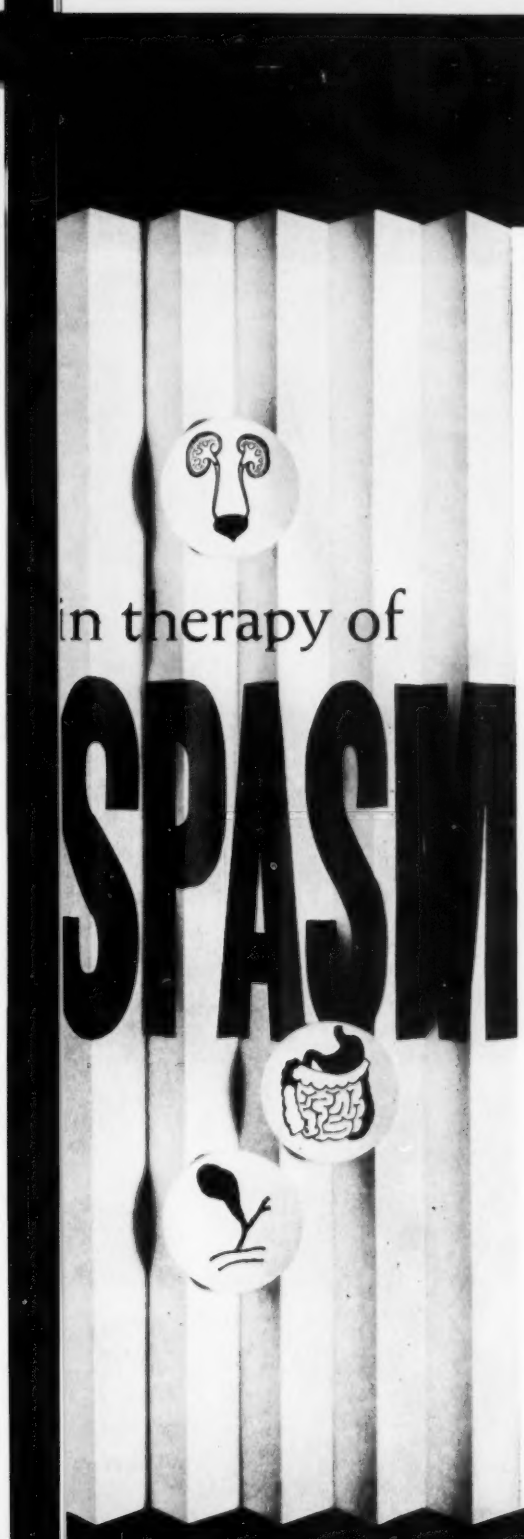


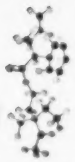

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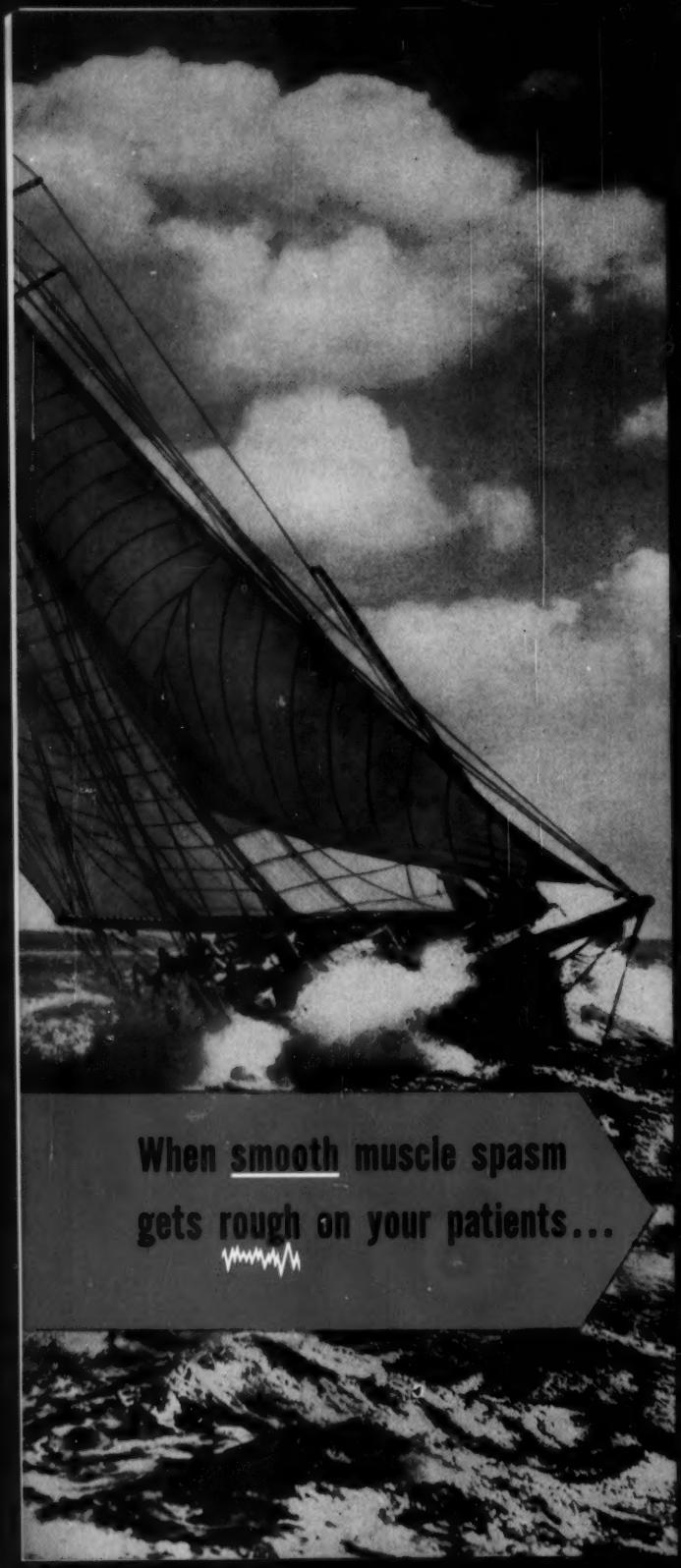
1. Berndt, R.: Arzneimittel-Forsch. 5:711 (Dec.) 1955.
2. Peiser, U.: Med. Klin. 50:1479 (Sept. 2) 1955.
3. Winter, H.: Medizinische, p. 1206 (Aug. 27) 1955.



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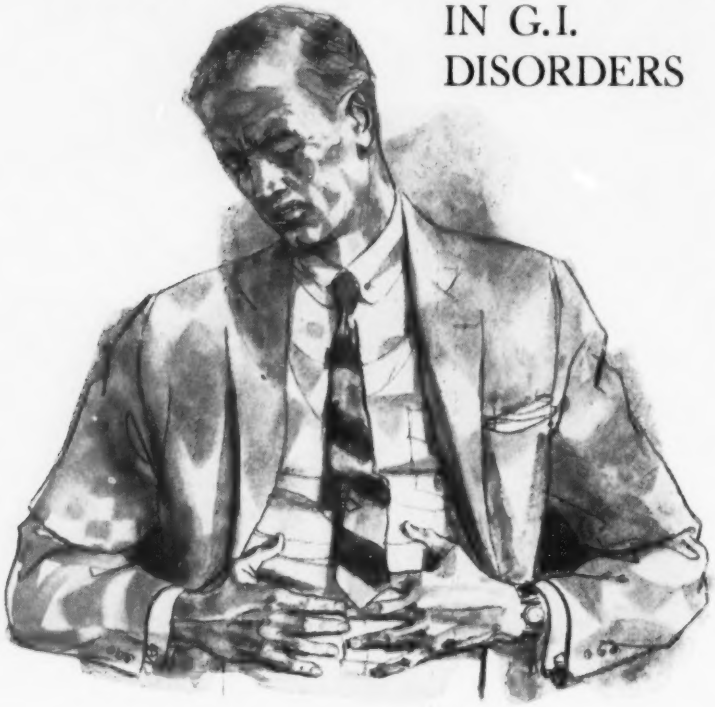

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1. Phillips, R. E.: Am. Pract. & Digest Treat. 7:1573, Oct. 1956. 2. Selling, L. S.: J.A.M.A. 157:1594, April 30, 1955. 3. Altschul, A. and Billow, B.: New York J. Med. 57:2361, July 15, 1957. 4. Ross, S. T.: Postgrad. Med. 23:24, Jan. 1958. 5. Tacket, H. S.: Am. Pract. & Digest Treat. 8:597, April 1957. 6. Bodi, T., Wirts, C. W., Jr. and Menduke, H.: Am. J. Gastroenterol. 29:643, June 1958.

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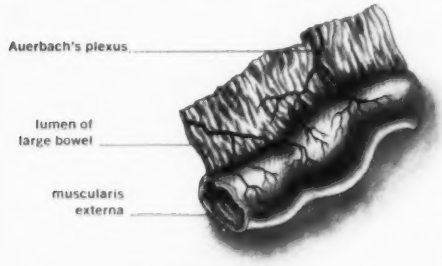


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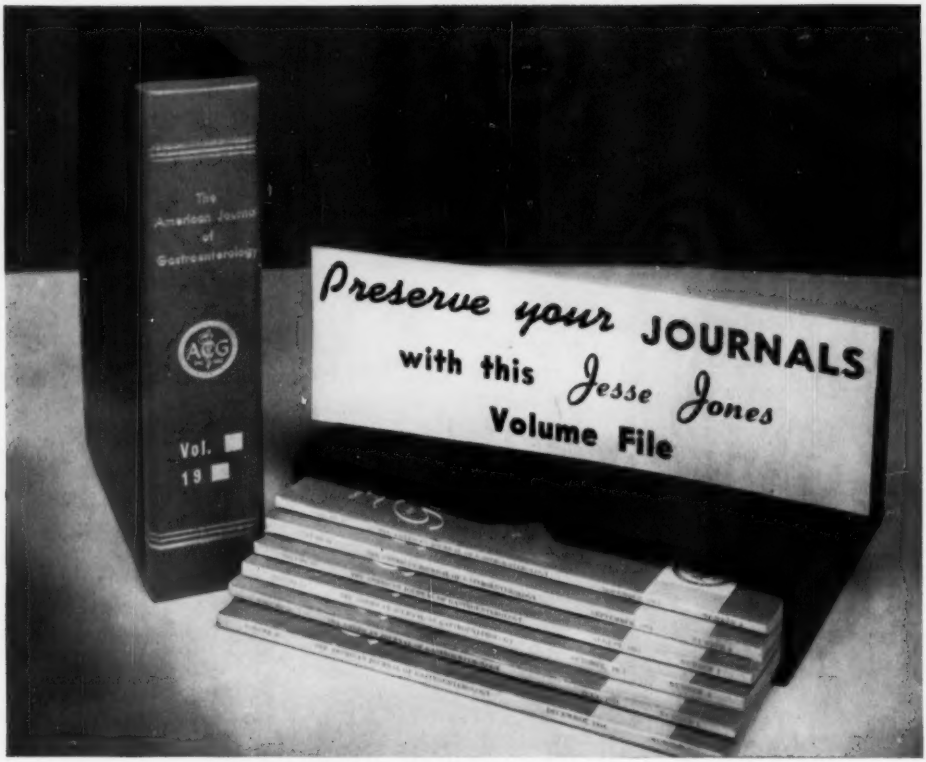


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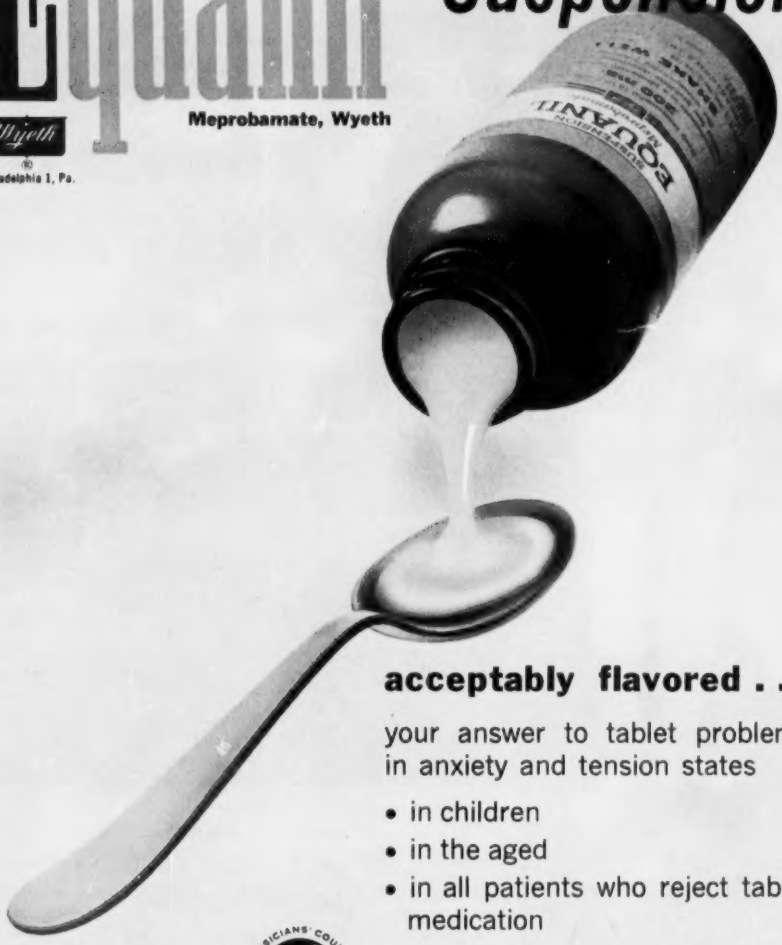


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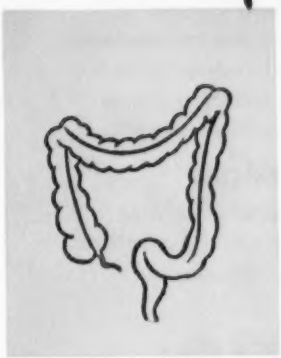

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(1) Kleckner, M. S., Jr.: J. Louisiana M. Soc. *108*:359, 1956. (2) Riese, J. A.: Am. J. Gastroenterol. *28*:541, 1957. (3) Settel, E.: J. Am. Geriatrics Soc., in press.

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DEXAMETHASONE

**to treat more patients more effectively**

In clinical trials with some 1,500 patients, glycosuria was noted in only two, transitory glycosuria in another two, and flattening of the glucose tolerance curve in one. There were no instances of aggravation of existing diabetes, no increase in insulin requirements. Patients whose diabetes was severely aggravated on prednisolone showed good tolerance when transferred to DECADRON.

MORE patients can be treated with DECADRON than with other corticosteroids, because in addition to being practically free of diabetogenic activity, therapy with DECADRON is also practically free of sodium retention, potassium depletion, hypertension, edema and psychic disturbances. Cushingoid effects are fewer and milder. DECADRON has not caused any new or "peculiar" reactions, and has produced neither euphoria nor depression, but helps restore a "natural" sense of well-being.

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